ORIGINAL ARTICLE

A C G publications

Org. Commun. 15:2 (2022) 204-211

organic communications

Solvent-free synthesis, molecular simulation and cytotoxicity of 1,4-benzodiazepine-2,5-diones

Abbas Khaja Mohideen [1], Kasim Mohammed Mustaque [1], Ismail Salim Meeran [1], Annadurai Subramani [2], V. S. Jamal Ahamed [1], Habeebullah Thajudeen [1] and Timiri Khudus Shabeer [1*]

[1]*Department of Chemistry, The New College, Chennai-600014, Tamilnadu, India*
[2]*Department of Chemistry, Apollo Arts and Science College, Chennai-602105, Tamilnadu, India*

(Received March 17, 2022; Revised June 17, 2022; Accepted June 18, 2022)

Abstract: The reaction of anthranilic acid with proline or pipecolinic methyl ester hydrochloride in presence of 1,1'-Carbonyldiimidazole (CDI) on oil bath heating under solvent-free condition afforded 1,4-benzodiazepine-2,5-dione (BZD) derivatives in moderate to good yields. Operational simplicity, absence of hazardous solvents, utility of an inexpensive coupling reagent (CDI) and mild reaction conditions are the significant advantages of this methodology. The cytotoxic activity of six BZDs were evaluated against HCT15 (Human Colon adenocarcinoma), SKMel2 (Human Skin Melanoma) and SKOV3 (Human Ovarian adenocarcinoma) cell lines. Compound 4b with *para* substituted chlorine atom showed moderate cytotoxicity against HCT15, SKMel2 and SKOV3 with IC_{50} values 37.04 ± 1.13, 39.45 ± 0.77 and 36.61 ± 0.10 µg/mL respectively. The comprehensive analysis of the interaction between 4a to 4f with receptor VEGFR-2 kinase, the result shows compound 4b have higher molecular docking score with receptor. These result well matched with the result of cytotoxicity.

Keywords: 1,4-Benzodiazepine-2,5-diones; solvent-free synthesis; cytotoxicity; molecular simulation.

1. Introduction

1,4-Benzodiazepine-2,5-diones (BZD), being seven-membered heterocycle lactam with privileged structural motifs, have been explored greatly for their biological activities. In medicinal chemistry, this significant structural scaffold is responsible for the bioactivity of many drug molecules. For instance, Diazepam (Valium), Lotrafiban and Abbeymycin are potent drugs of the BZD family and are well-known for their psychopharmacological properties[1-3]. Additionally, the physicochemical properties of these molecules are regarded as novel peptidomimetic and prevailed active framework in many therapeutics[4-6]. Although, the careful literature search related to BZD, the scifinder exactly showed only 129 entries including very few synthetic routes[7-9]. Hence, the search for mild methodologies for the preparation of BZD is an increasingly important challenge for organic chemists.

Some bio-active molecules, for instance, Circumdatins A-J possess both quinazoline and benzodiazepine moieties which are considered to be useful chemotaxonomic markers. Owing to the distinct synthetic and biological significance of BZD derivatives, it is indispensable to divulge new strategies for their synthesis. As a part of our continued interest in exploring the synthetic strategy of heterocycles using greener methodologies, we recently reported one-pot synthesis of

* Corresponding author: E-Mail: shabeer@thenewcollege.edu.in

Thearticlewaspublishedby ACG Publications
http://www.acgpubs.org/journal/organic-communications © April-June 2022 EISSN:1307-6175
DOI:http://doi.org/10.25135/acg.oc.133.2203.2388
Available online: June 28, 2022

dihydroquinazolinones via the cyclocondensation of 2-aminobenzamide with aromatic aldehydes and ketone in water[10]. In this context, we report a novel approach for the synthesis of 1,4-benzodiazepine-2,5-dione derivatives from substituted anthranilic acids and α-amino acid methyl esters as starting materials in a one-pot two-step protocol.

2. Experimental

2.1. General

All commercially available reagents were purchased from Sigma and were used without further purification. Silica gel 60 (230 – 400 mesh, 50 id × 270 mm, Merck) was used for column chromatography. NMR spectra (δ, ppm) were recorded on a Varian Mercury 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz) Spectrometer (Varian Inc) referenced to the residual peaks of CDCl3 at δ = 7.26 and 77.24 for ^{1}H- and ^{13}C-NMR, respectively.

2.2. Chemistry

*2.2.1. Synthesis of 1,4-benzodiazepine-2,5-diones derivatives (**4a-f**)*

Anthranilic acid 0.137 g (1 mmol) was mixed with CDI 0.243 g (1.5 mmol) heated on oil bath for 3 mins. To the melted reaction mixture, proline methyl ester hydrochloride, 0.165 g (1 mmol) was added and heating was continued for seven minutes. The formation of the product was confirmed by thin layer chromatography (EA:Hex – 2:8). The reaction mixture was cooled to RT and ethyl acetate was added to the crude product, washed with brine solution, dried and purified by column chromatography.

2.2.2. Spectral Characterization of Selected Compounds

*2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazpine-5,11(10H,11aH)-dione (**4a**)*: Yield: 75%, White crystalline solid; M.P. = 220 °C; ^{1}H NMR (DMSO-d6): δ (ppm) 10.48 (s, 1H, -NH), 7.77 (d, 1H, Ar-H, *J = 7.6 Hz*), 7.49 (t, 1H, Ar-H, *J* = 6.8 Hz), 7.22-7.21 (m, 1H, Ar-H), 7.10 (d, 1H, Ar-H, *J* = 8 Hz), 4.09 (t, 1H, *J* = 6.4 Hz), 3.75-3.54 (m, 1H), 3.46-3.39 (m, 1H), 2.48-2.46 (m, 1H), 1.95-1.76 (m, 3H); ^{13}C NMR (DMSO-d6): δ (ppm) 171.1, 164.9, 136.8, 132.5, 130.7, 127.0, 124.2, 121.7, 56.6, 47.3, 26.2, 23.5.

*8-chloro-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**4b**)*: Yield: 59%, White solid; M.P. = 222-225 °C; ^{1}H NMR ($CDCl_3$): δ (ppm) 9.09 (s, 1H, -NH), 7.95 (d, 1H, Ar-H, *J* = 8 Hz), 7.25 (dd, 1H, Ar-H, *J* = 2.4 & 6.0 Hz), 7.07 (d, 1H, Ar-H, *J* = 1.6 Hz), 4.06 (t, 1H, *J* = 7.8 Hz), 3.81-3.78 (m, 1H), 3.60-3.57 (m, 1H), 2.78-2.76 (m, 1H), 2.10-1.92 (m, 3H); ^{13}C NMR ($CDCl_3$): δ (ppm) 171.2, 164.6, 138.2, 136.3, 132.6, 125.4, 125.3, 120.9, 56.7, 47.4, 26.2, 23.4.

*8-methoxy-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**4c**)*: Yield: 63%, White solid; ^{1}H NMR ($CDCl_3$): δ (ppm) 7.93 (s, 1H, -NH), 7.54 (dd, 1H, Ar-H, *J* = 7.6 and 1.2 Hz), 7.17 (t, 1H, Ar-H, *J* = 8 Hz), 7.00 (dd, 1H, Ar-H, *J* = 8.4 and 1.2 Hz), 4.03 (t, 1H, *J* = 5.6 Hz), 3.88 (s, 3H, OCH3), 3.82-3.77 (m, 1H), 3.62-3.55 (m, 1H), 2.76-2.73 (m, 1H), 2.03-1.97 (m, 3H)

*8-nitro-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**4d**)*: Yield: 57%, Light yellow solid; M.P. = 246-248 °C; ^{1}H NMR ($CDCl_3$): δ (ppm) 8.57 (s, 1H, -NH), 8.21 (d, 1H, Ar-H, *J* = 8.8 Hz), 8.08 (dd, 1H, Ar-H, *J* = 2.4 & 6.0 Hz), 7.92 (d, 1H, Ar-H, *J* = 1.6 Hz), 4.11 (t, 1H, *J* = 7.8 Hz), 3.92-3.85 (m, 1H), 3.67-3.60 (m, 1H), 2.83-2.80 (m, 1H), 2.14-2.04 (m, 3H); ^{13}C NMR ($CDCl_3$): δ (ppm) 170.5, 163.8, 136.2, 13.3, 132.0, 119.3, 116.3, 116.2, 56.6, 47.7, 26.3, 23.3

*7,8,9,10-tetrahydrobenzo[e]pyrido[1,2-a][1,4]diazepine-6,12(5H,6aH)-dione (**4e**)*: Yield: 73%, White crystalline solid; M.P. = 225-227 °C; ^{1}H NMR ($CDCl_3$): δ (ppm) 8.52 (s, 1H, -NH), 7.91 (dd, 1H, Ar-H, *J* = 7.6 and1.2 Hz), 7.46 (td, 1H, Ar-H, *J*=14, 7.6 & 1.2 Hz), 7.26-7.22 (m, 1H, Ar-H), 6.95 (d, 1H, Ar-

H, *J* = 7.6 Hz) 4.56-4.50 (m, 1H), 4.14 (dd, 1H, *J* = 6.4 & 2.8 Hz), 3.03-2.95 (m, 1H), 2.26-2.21 (m, 1H), 1.97-1.91 (m, 1H), 1.87-1.81 (m, 1H), 1.75-1.56 (m, 3H); HR-ESI-TOF-MS:*m/z* $[M+H]^+$=231.1146 (calcd. 231.1135)

3-methoxy-7,8,9,10-tetrahydrobenzo[e]pyrido[1,2-a][1,4]diazepine-6,12(5H,6aH)-dione (***4f***): Yield: 61%, White solid; ^{1}H NMR ($CDCl_3$): δ (ppm) 7.82 (s, 1H, -NH), 7.48 (d, 1H, Ar-H, *J* = 6.8 Hz), 7.17 (t, 1H, Ar-H, *J* = 8 Hz), 6.97 (d, 1H, Ar-H, *J* = 6.8 Hz), 4.54-4.49 (m, 1H), 4.13 (t, 1H, Ar-H, *J* = 6.8 Hz), 3.88 (s, 3H, OCH_3), 3.03-2.95 (m, 1H), 2.26-2.22 (m, 1H), 1.96-1.90 (m, 1H), 1.86-1.81 (m, 1H), 1.75-1.57 (m, 3H)

2.3. Biological Assay

2.3.1. Cytotoxicity Assay

The cell lines HCT15 (Human Colon adenocarcinoma), SKMel2 (Human Skin Melanoma) and SKOV3 (Human Ovarian adenocarcinoma) cell lines were purchased from Korean Cell Line Bank (Chongno-gu, Seoul, Republic of Korea). Cells were cultured in RPMI-1640 media, supplemented with 10% heat-inactivated fetal bovine serum (FBS), 1mM $NaHCO_3$, 2mM L-glutamine. All cell lines were maintained in culture at 37 °C in an atmosphere of 5% CO_2.

Cells were thawed in 96-well plate (10^4 cells/well) for 24 h. Tested compounds were dissolved in DMSO. Different concentration of the compound under test (1.56, 3.12, 6.25, 12.5, 25, 50 µg/mL) was added to the cell monolayer. Triplicate wells were prepared for each individual concentration. The cytotoxicity assay was done against HCT-15 (1 x 10^5 cells/mL), SK-Mel-2 (1 x 10^5 cells/mL) and SK-OV-3 (1 x 10^5 cells/mL) and cell lines using a colorimetric SRB assay method[12].Growing cells were harvested and suspended in the culture media (100 µL, RPMI-1640) in a 96-well plate. After 24 h of incubation at 37 ºC in humidified 5% CO_2, the cells were treated with varying concentrations of test compounds (100 µL) and incubated further for 48 h under the same conditions. The cells were attached with 50% trichloroacetic acid and stained for 30 minutes with SRB. The unbound dye was washed with 1% acetic acid, and the protein-bound dye was extracted with 10 mMtris base (pH 10.5) for 5 min. The optical density was measured at 520 nm in a micro plate reader to determine cell growth inhibition. The results were expressed as the concentration at which there was 50% inhibition (IC_{50}).

2.3.2. Molecular Docking with VEGFR2 (Vascular Endothelial Growth Factor Receptor 2)

Vascular endothelial growth factor-A (VEGF-A, also known as vascular permeability factor) is a major factor in regulating functions of endothelial cells in vasculogenesis and angiogenesis. Vascular endothelial growth factor, as a ligand, executes its functions through VEGF receptors. In humans, there are at least three VEGF receptors, VEGFR-1, VEGFR-2, and VEGFR-3. VEGFR-2 is the principal VEGFR in humans. It is abundantly expressed in lymphatic endothelial cells and vascular endothelial cells. VEGFR-2 is also expressed in neuronal cells, hematopoietic stem cells, megakaryocytes and different cancer cells.

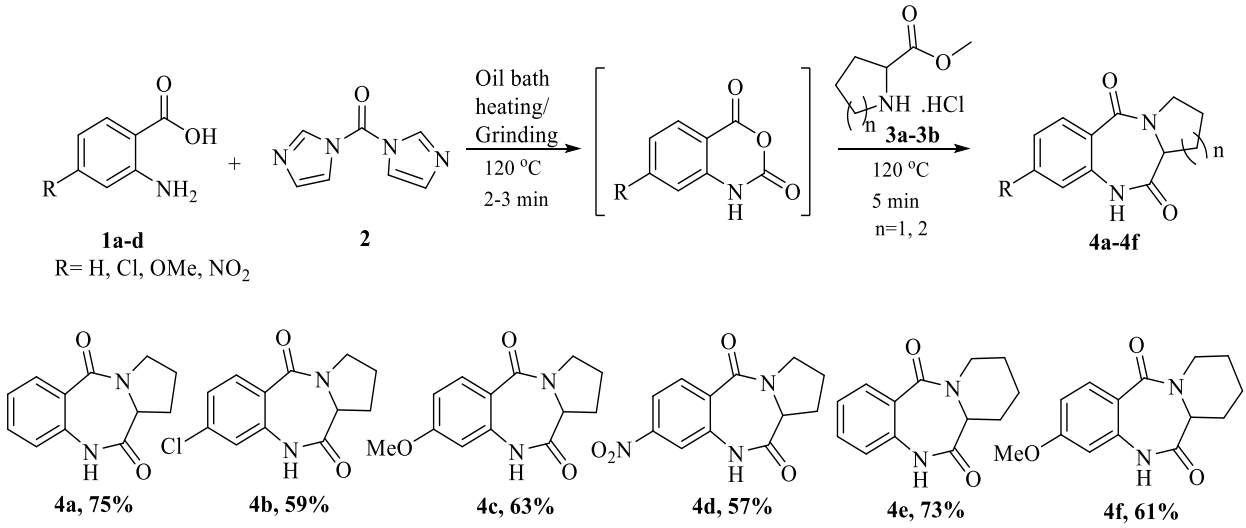
Molecular docking was performed using Auto Dock Tools (ADT version 1.5.7) and Auto Dock docking programs (version 4.2.5.1). The rigid docking is based on the genetic algorithm. The 3D structure of VEGFR-2 kinase receptor (PDB code: 2XIR) was downloaded from the protein data bank (http://www.rcsb.org./pdb). The 2D chemdraw structures BZD compounds were converted into energy optimized structures by Chem 3D 17.0. and saved as pdb file. The protein and ligands' pdb files were prepared using AD tools. The protein was bounded in a grid box with dimensions of 90 × 90 × 90 grid points in x × y × z directions with 0.378 Å spacing. The dock results were derived from the dock extension file 'dlg'. Based on the docking scores of each pose, the lowest energy conformer was selected as the best binding mode. Discovery studio and PyMOL v0.990 molecular graphics softwares were used to visualize the docking conformations.

3. Results and Discussion

3.1. Chemistry

At the beginning, we studied the model reaction in solvent-free condition for the synthesis of BZD using anthranilic acid and proline methyl ester hydrochloride as starting materials (scheme 1). In this reaction, anthranilic acid was mixed with CDI and heated on oil bath for 2 mins. To the melted reaction mixture, proline methyl ester hydrochloride was added and heating was continued for five more minutes to yield BZD. The formation of the product was confirmed by thin layer chromatography. Ethyl acetate was added to the crude product, washed with brine solution, dried and purified by column chromatography.

Utilizing CDI as a coupling reagent, our primary aim was to accomplish the amidation reaction between anthranilic acid and proline methyl ester hydrochloride in solvent-free condition. Surprisingly, as a striking remark we destined with the unprecedented formation of BZD. To our knowledge, there is no report on the synthesis of title compound using CDI in solvent-free condition. Hence, with the intention of reducing the environmental impacts of solvent-based methods, the BZD preparation was explored using both grinding and solvent-free heating methods.



Scheme 1. The synthesis of 1,4-benzodiazepine-2,5-diones from anthranilic acid and CDI

Table.1 Optimization of temperature time and methods

Entry	Temp.(°C)	Time (min)	Methods*	Yield (%)[a]
1	rt	10	grinding	38
2	rt	20	grinding	48
3	rt	30	grinding	51
4	60	60	oil bath	trace
5	90	60	oil bath	45
6	120	60	oil bath	75
7	120	30	oil bath	76
8	120	10	oil bath	75

**General Procedure:* Anthranilic acid (1 mmol) was mixed with CDI (1.5 mmol) heated on oil bath for 3 mins. To the melted reaction mixture, proline methyl ester hydrochloride (1 mmol) was added and heating was continued for required time. *a*- Isolated yield, *rt*- room temperature

Solvent-free synthesis of 1,4-benzodiazepine-2,5-diones

In order to optimize the reaction conditions, we carried out several screening experiments by varying time and temperature (Table 1). BZD was obtained in moderate yields when the reaction was carried out at room temperature by means of grinding (Table 1, entry 1, 2 and 3). Extending the time of grinding for 30 mins, yield of the product was not much improved (Table 1, entry 3). With a way to enhance the product yield, in the absence of solvent, the reaction was brought off in oil bath heating.

Careful inspection of TLC revealed traces of product at 60 ^{o}C and 45% at 90 ^{o}C for a time period of 60 mins (Table 1, entry 4 and 5). To our contentment, an increased product yield of 75% was obtained at 120 ^{o}C in 10 mins. (Table 1, entry 8). Hence, the above optimized condition was used to synthesize BZD derivatives.

We ardently believe the *in-situ* formation of isatoic anhydride in the first step as an intermediate from anthranilic acid and CDI. It is evident from the literature, the BZD derivatives were synthesized using isatoic anhydride and alpha amino acids[11]. To generalize this scheme for the synthesis of BZD derivatives, the reaction was executed with various substituted anthranilic acids (**1a-d**) with proline (**3a**) and pipecolinic acid methyl ester hydrochloride (3b). The yields of the synthesized compounds **4a–f** (57–75%) are outlined in Scheme 1.

3.2. Biological Assay

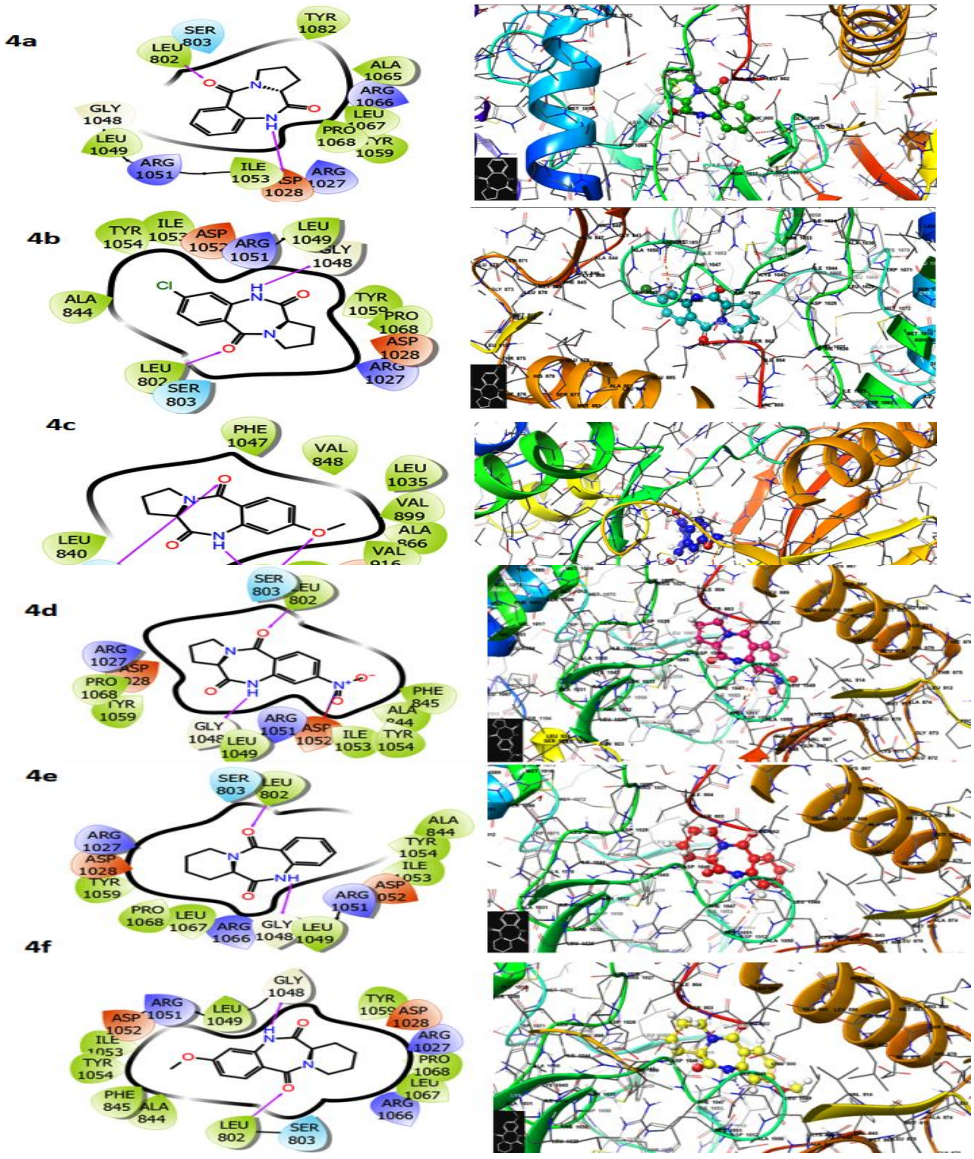


Figure 1. Molecular simulation 2D and 3D structures of compounds; 4a to 4f with VEGFR-2 kinase

3.2.1. Cytotoxicity

To evaluate the cytotoxicity of synthesized compounds, three different cancer cell lines were used: HCT15 (Human Colon adenocarcinoma), SKMel2 (Human Skin Melanoma), and SKOV3 (Human Ovarian adenocarcinoma). The in vitro SRB (Sulforhodamine B) assay was used to assess the viability of the cells.

Cisplatin was used as a positive control. All experiments were carried out in triplicate and the anticancer efficacy value of the synthesized compounds were indicated by IC_{50} values (the concentration that causes a 50% inhibition of the cell growth) and was calculated by linear regression analysis, expressed in mean ± SD. The investigation of compound 8-chloro-2,3-dihydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H,11aH)-dione (**4b**) containing chlorine atom at C8 position exhibited a moderate cytotoxicity against HCT15, SKMel2, SKOV3 cell lines with IC_{50} values 27.04 ± 1.13, 29.45 ± 0.77 and 26.61 ± 0.10 µg/mL respectively. Other compounds were not active against all three cell lines even at the concentration of 50 µg/mL.

Compounds	**Docking score kcal.mol^{-1}**	**Active sites with a mode of interaction**	
		H-bond	**Hydrophobic contacts (at 4Å)**
4a	-6.339	LEU 802 ASP 1028	LEU 802, TYR 1082, ALA 1065, LEU 1067, PRO 1068, ILE 1053, LEU 1049
4b	-6.959	LEU 802 GLY 1048	TYR 1054, ILE 1053, LEU 1049, TYR 1059, PRO 1068, LEU 802, ALA 844
4c	-6.452	ASN 923 CYS 919 (-NH) CYS 919 (-OCH_3)	PHE 1047, VAL 848, LEU 1035, VAL 899, ALA 866, VAL 916, PHE 918, CYS 919, LEU 840
4d	-6.603	LEU 802 GLY 1048	LEU 802, PRO 1068, TYR 1059, LEU 1049, ILE 1053, TYR 1054, ALA 844, PHE 845
4e	-6.594	LEU 802 GLY 1048	LEU 802, TYR 1059, PRO 1068, LEU 1067, LEU 1049, ILE 1053, TYR 1054, ALA 844
4f	-6.59	LEU 802 GLY 1048	TYR 1059, PRO 1068, LEU 802, ALA 844, PHE 845, TYR 1054, ILE 1053, LEU 1049

Table 2. Docking analysis of synthesized compounds (4a-f) against *VEGFR-2 kinase* protein

3.2.2. Validation on the Active Sites of VEGFR-2 Kinase

Molecular docking study is an attractive scaffold to understand the synthesized compounds-protein interactions, which can corroborate our experimental results. The best interaction site of

compounds with target protein visualized in Figure 1 and data were summarized in Table.2 The observed docking scores of compounds 4a to 4f are -6.339, -6.959, -6.452, -6.603, -6.594 and -6.59 kcal/mol respectively. The docking score results revealed that all compounds were well located in the hydrophobic sites and strongly interact with VEGFR-2 kinase receptor via π-π stacking, hydrophobic and hydrogen bonding interactions. The compound 4b showed the highest docking score which was influenced by hydrogen bonding with residues LEU 802, GLY 1048 and hydrophobic contacts like TYR 1054, ILE 1053, LEU 1049, TYR 1059, PRO 1068, LEU 802, ALA 844. By the above facts, the compound 4b strongly binding and regulate the VEGFR-2 kinase activity in therapeutic strategies and cancer prevention. These results were well matched with the result of cytotoxicity of compound 4b.

4. Conclusion

In conclusion, a rapid access to an unprecedented class of BZD derivatives through a robust and convenient synthetic pathway has been achieved. To screening cytotoxicity against HCT15, SKMel2, SKOV3 cell lines with IC_{50} values 37.04 ± 1.13, 39.45 ± 0.77 and 36.61 ± 0.10 µg/mL respectively, the compound 4b moderately active against all the tested cell lines. The molecular docking result compound 4b has higher docking score with VEGFR-2 in breast cancer protein. By the way, this synthetic strategy substantiates an efficient one-pot two-step greener process to obtain the desirable benzodiazepine moieties that can be acclaimed in a wide range of psychopharmaceutical drugs on the market.

Acknowledgements

We gratefully acknowledge the financial support from UGC project (MRP-5993/15, Comcode: TNMD043).

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

ORCID
Abbas Khaja Mohideen: 0000-0003-3393-067X
Kasim Mohammed Mustaque: 0000-0003-4037-6603
Ismail Salim Meeran: 0000-0002-1635-4175
Annadurai Subramani: 0000-0002-0851-268X
V. S. Jamal Ahamed: 0000-0003-4011-8911
Habeebullah Thajudeen: 0000-0001-5973-2474
Timiri Khudus Shabeer: 0000-0001-7790-3388

References

[1] Araújo, A.C.; Nicotra,F.;Airoldi, C.;Costa, B.;Giagnoni, G.; Fumagalli, P.; Cipolla, L. Synthesis and biological evaluation of novel rigid 1,4-benzodiazepine-2,5-dione chimeric scaffolds. *Eur. J. Org. Chem.* **2008**, *2008*, 635-639.

[2] Leonard, K.;Marugan, J.J.;Raboisson, P.; Calvo, R.;Gushue, J.M.;Koblish, H.K.;Lattanze, J.; Zhao, S.; Cummings, M.D.; Player, M.R.; Maroney, A.C.Novel 1,4-benzodiazepine-2,5-diones as Hdm2 antagonists with improved cellular activity. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3463-3468.

[3] Parks, D.J.; LaFrance, L.V.; Calvo, R.R.; Milkiewicz, K.L.; Gupta, V.; Lattanze, J.; Ramachandren, K.; Carver, T.E.; Petrella, E.C.; Cummings, M.D.; Maguire, D.1,4-Benzodiazepine-2,5-diones as small molecule antagonists of the HDM2–p53 interaction: discovery and SAR. *Bioorg. Med.Chem. Lett.* **2005**. *15*, 765-770.

[4] Calcaterra, N. E.; Barrow, J.C. Classics in chemical Nneuroscience: diazepam (Valium). *ACS Chem. Neurosci.* **2014**, *5*, 253-260.

[5] Scarborough, R. M.; Gretler, D.D. Platelet glycoprotein IIb-IIIa antagonists as prototypical integrin blockers: Novel parenteral and potential oral antithrombotic agents. *J. Med. Chem.* **2000**, *43*, 3453-3473.

[6] Hochlowski, E.E.; Andres, W.W.; Theriault, R.J.; Jackson, M.; Mcalpine, J.B. Abbeymycin, a new anthramycin-type antibiotic produced by a streptomycete. *J. Antibiot.* **1987**, *40*, 145-148.

[7] Anil, S.M.; Shobith, R.; Kiran, K.R.; Swaroop, T.R.; Mallesha, N.; Sadashiva, M.P. Facile synthesis of 1,4-benzodiazepine-2,5-diones and quinazolinones from amino acids as anti-tubercular agents. *New J.Chem.* **2019**, *43*, 182-187.

[8] Pettersson, B.; Hasimbegovic, V.; Bergman, J. Total synthesis of fuligocandines A and B. *Tetrahedron Lett.* **2010**, *51*, 238-239.

[9] Jadidi, K.; Ghahremanzadeh, R.; Asgari, D.; Eslami, P.; Arvin-Nezhad, H. Eco-friendly synthesis of 1,4-benzodiazepine-2,5- diones in the ionic liquid Br. *Monatsh. Chem.* **2008**, *139*, 1229-1232.

[10] Mustaque, K.M.; Subramani, A.; Shabeer, T.K.; Thajudeen, H.; Jamal Ahamed, V.S. Amino acid catalyzed synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives. *Lett. Org. Chem.* **2018,** *15*, 246-250.

[11] De La Cruz, A.; Vega-Acevedo, C. A.; Rivero, I.; Chávez, D. J. Improved method for microwave-assisted synthesis of benzodiazepine-2,5-diones from isatoic anhydrides mediated by glacial acetic acid. *J. Braz. Chem. Soc.* **2018,** *29*, 1607-1611.

[12] Rahman, M. A. A.; Cho, S. C.; Song, J.; Mun, H. T.; Moon, S. S. Dendrazawaynes A and B, antifungal polyacetylenes from *Dendranthema zawadskii* (Asteraceae). *Planta Med.* **2007,** *73*, 1089-1094.