# Design, Development and Molecular Docking Studies of C-2 Sulfenylated Benzofurans: Potential Interleukin 1-β Antagonist

Jyoti[1], Suman Devi[1], Vikram Kumar[2] and Deepak Wadhwa[1,*]

[1]Department of Chemistry, Chaudhary Bansi Lal University, Bhiwani-127021, India
[2]Department of Chemistry, I.B. College, Panipat-132103, India

*Corresponding author: E-mail: deepak_chem08@cblu.ac.in

An environmental friendly methodology for C-2 sulfenylation of benzofurans through dehydrogenative cross-coupling has been developed. Sulfenylation at second position is carried out using commercially available thiols in presence of molecular iodine and DMSO. The reaction accommodates wide spectrum of electronically diverse substituents on thiophenol ring. This process offers diverse advantages, including greener reaction conditions, moderate to good percentage yields, easy workup, no additional metal catalysts requirement and gram scale synthesis. Molecular docking studies is also conducted to substantiate interleukin 1-β antagonist nature of the designed compounds.

**Keywords: Benzofuran, Sulfenylation, Thiophenol, Iodine, DMSO.**

## INTRODUCTION

Benzofurans are found as core heterocycle in various physiologically active natural and synthetic medicines as well as other materials [1,2]. These compounds exhibit diverse biological properties including antitumor, antibacterial [3], antioxidative [4], anti-AD, antiparasitic [5], anti-acetylcholine [6] and anti-inflammatory [7]. Additionally, benzofurans can function as a bone anabolic agent [1] and a fluorescent analgesic sensor [8,9]. These compounds are common in higher plant families, with Asteraceae, Rutaceae, Liliaceae and Cyperaceae being rich in benzofuran moiety. Noteworthy that benzofuran moiety found in the Asteraceae family [10], a natural product include ailanthoidol, amiodarone and bufuralol molecules. Various 2-arylbenzofuran derivatives, recovered from natural sources, exhibit biological activities, like anticancer, antimicrobial [11], anti-inflammatory, antifungal [12], antihelmantic [13], anti-oxidative [2] and antibacterial [3] properties. Recently, an oral active and blood-brain barrier-permeable benzofuran analogue with anti-amyloid aggregation activity, has been discovered suggesting a potential remedy for Alzheimer's disease [14]. Moreover, addition of a thioether link to such a possible moiety also makes the molecule far more potent.

In past decades, considerable efforts have been put forth into developing novel techniques for construction of C–S bonds. Transition-metal free cross-coupling is one of most effective method in forming C–S bonds. Existing methods for sulfenylation of benzofuran in the literature often rely on transition metal catalysts or pre-functionalized benzofuran ring [15,16]. Cspeds *et al.* [17] reported C-2 sulfenylation using disulfide presence and Pd catalyst and Zhen *et al.* [18] communicated direct halo-sulfenylation of benzofurans using disulfides and *N*-bromosuccinimide (NBS). Motivated by this inspiration, a protocol for direct C-H sulfenylation at C-2 position of benzofuran using molecular iodine and DMSO in open atmosphere is developed.

## EXPERIMENTAL

All the reactions were conducted in oven dry round bottom flask and in open atmosphere. Commercially available chemicals were utilized as such as received from Sigma-Aldrich, Alfa Aesar and TCI. Compounds were purified using 120-300 mesh silica gel in column chromatography. For characterization, ^{1}H & ^{13}C NMR spectra were recorded on a 300 MHz spectrometer, using CDCl_3 solvent and TMS as internal standard.

**General procedure for synthesis of C-2 thiolated benzo-furans:** A 25 mL round bottom flask containing magnetic bar was loaded with iodine (5 mg, 0.02 mmol), benzofuran (**1**) (0.2 mmol), thiols (**2**) (0.24 mmol) and DMSO (2 mL). The round bottom flask was then fitted with coil water condenser and further the reaction mixture was vigorously stirred under open atmos-phere at 80 °C for 8 h. After completion of the reaction, moni-tored with TLC, the resulting mixture was cooled down to room temperature. The excess of iodine was neutralized by adding dilute solution of sodium thiosulphate. Further, the obtained solid residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to obtain the desired product **3** (**Scheme-I**).

**2-(4-Bromophenylthio)benzofuran (3a):** ^{1}H NMR (CDCl$_3$, 300 MHz) δ ppm: 7.57-7.53 (m 1H), 7.46-7.45 (m, 1H), 7.43-7.36 (m, 3H), 7.33-7.30 (m, 1H), 7.23-7.20 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ ppm: 155.5, 145.5, 132.4, 132.3, 131.1, 128.1, 126.8, 123.8, 121.6, 120.3, 111.8, 107.3; HRMS: *m/z* (ESI) calcd. for C$_{14}$H$_9$OSBr [M+H]$^+$ 305.95, 303.96; found 305.92, 303.82.
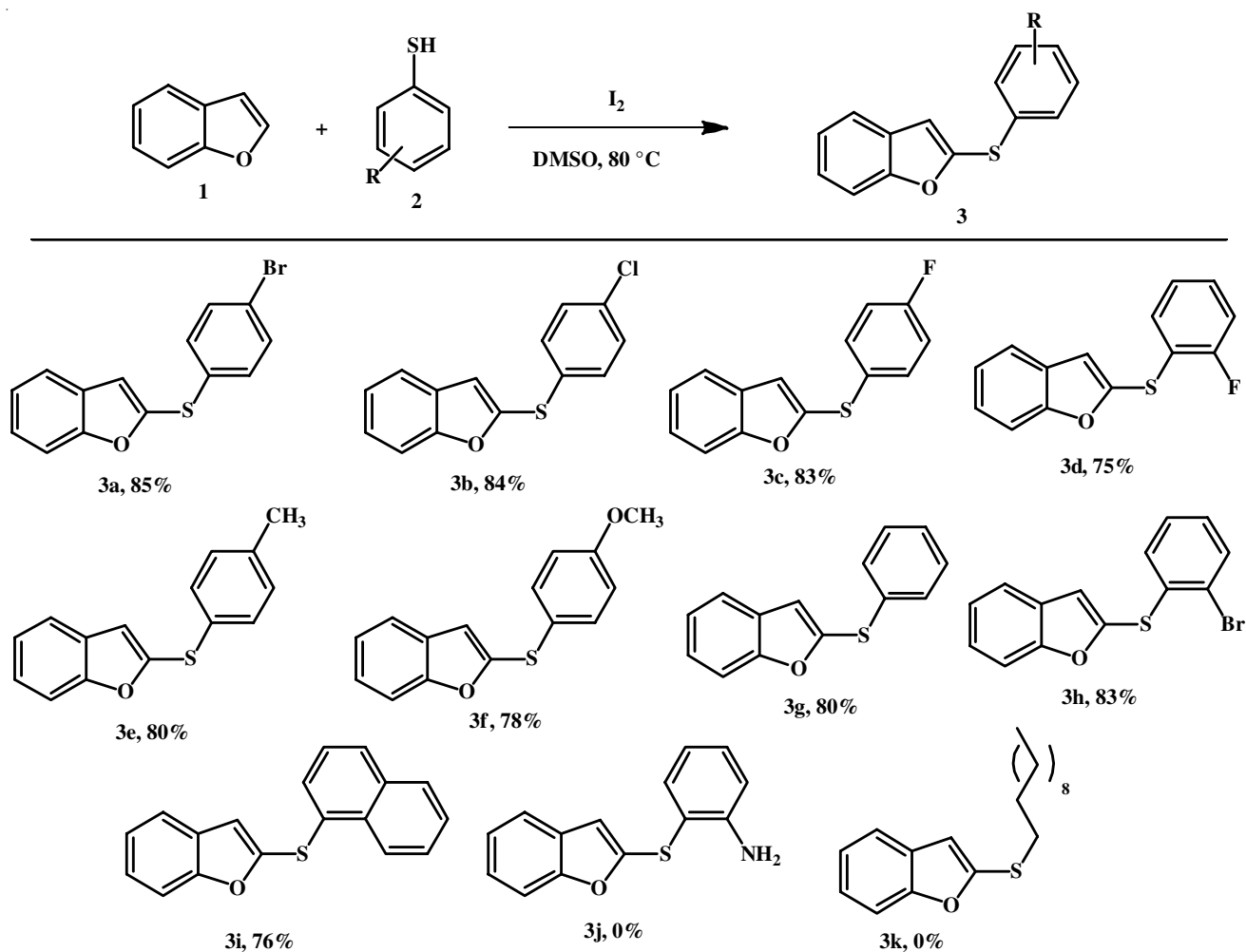
**2-((4-Chlorophenyl)thio)benzofuran (3b):** ^{1}H NMR (CDCl$_3$, 300 MHz) δ ppm: 7.59-7.56 (m, 1H), 7.48-7.44 (m, 1H), 7.36-7.32 (m, 1H), 7.31-7.23 (m, 6H), 7.06 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ ppm: 156.93, 147.30, 133.36, 132.88,

130.47, 129.50, 128.33, 125.55, 123.31, 121.16, 114.83, 111.55; HRMS: *m/z* (ESI) calcd. for C$_{14}$H$_9$OSCl [M+H]$^+$ 260.0063; found 260.0051.

**2-(4-Fluorophenylthio)benzofuran (3c):** ^{1}H NMR (CDCl$_3$, 300 MHz) δ ppm: 7.56 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.50 Hz, 1H), 7.42 (t, *J* = 7.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.25-7.22 (m, 1H), 7.10 (d, *J* = 7.50 Hz, 1H), 7.01 (d, *J* = 9.0 Hz, 1H), 6.97-6.90 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ ppm: 164.1, 162.1, 161.9, 155.6, 130.6, 132.5, 130.69, 130.5, 130.5, 128.1, 126.9, 124.5, 123.8, 122.7, 120.4, 116.0, 115.8, 114.5, 114.3, 114.0, 111.8; HRMS: *m/z* (ESI) calcd. for C$_{14}$H$_9$OSF [M+H]$^+$ 245.04; found 245.01.

**2-(2-Fluorophenylthio)benzofuran (3d):** ^{1}H NMR (CDCl$_3$, 300 MHz) δ ppm: 7.55-7.50 (m, 1H), 7.47-7.43 (m,1H), 7.40-7.36 (m, 1H), 7.35-7.30 (m, 1H), 7.25-7.20 (m, 2H), 7.14-7.00 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ ppm: 161.5, 159.5, 155.6, 144.6, 131.9, 128.2, 126.7, 124.8, 124.8, 123.8, 120.2, 116.2, 116.0, 111.8, 107.2, 100.0; HRMS: *m/z* (ESI) calcd. for C$_{14}$H$_9$OSF [M+H]$^+$ 245.04; found 245.01.

**2-((4-Methylphenyl)thio)benzofuran (3e):** ^{1}H NMR (CDCl$_3$, 300 MHz) δ ppm: 7.54-7.51 (m, 1H), 7.44-7.41 (m, 1H), 7.30-7.11 (m, 4H), 7.11-7.08 (m, 2H), 6.95 (d, *J* = 0.9 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ ppm: 156.77, 148.99, 137.60, 130.15, 130.06, 127.95, 125.07, 123.10, 120.90, 113.45,



**Scheme-I:** Substrate scope for C-2 sulfenylation of benzofuran

111.44, 21.20; HRMS: *m/z* (ESI) calcd. for $C_{15}H_{12}OS$ [M+H]$^+$ 241.06; found 241.01.

**2-(4-Methoxyphenylthio)benzofuran (3f):** ^{1}H NMR (CDCl$_3$, 300 MHz) δ ppm: 7.59 (s, 1H), 7.46-7.40 (m, 3H), 7.37-7.30 (m, 2H), 7.14 (s, 1H), 6.88-6.82 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ ppm: 160.1, 155.2, 148.8, 133.7, 127.5, 127.1, 122.1, 120.9, 119.7, 115.0, 104.0, 55.4; HRMS: *m/z* (ESI) calcd. for $C_{15}H_{12}O_2S$ [M+H]$^+$ 257.06; found 257.01.

**2-(Phenylthio)benzofuran (3g):** ^{1}H NMR (CDCl$_3$, 300 MHz) δ ppm: 7.55-7.40 (m, 1H), 7.47-7.40 (m, 3H), 7.40-7.35 (m, 1H), 7.35-7.28 (m, 3H), 7.23-7.14 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ ppm: 152.9, 135.2, 132.9, 130.6, 129.3, 129.0, 128.0, 127.7, 126.2, 125.8, 120.6, 116.7, 111.6; HRMS: *m/z* (ESI) calcd. for $C_{14}H_{10}OS$ [M+H]$^+$ 227.05; found 227.03.

**2-((2-Bromophenyl)thio)benzofuran (3h):** ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm: 7.64-7.61 (m, 1H), 7.58-7,48 (m, 2H), 7.42-7.34 (m, 1H), 7.32-7.25 (m, 1H), 26 7.20-7.18 (m, 1H), 7.15-7.13 (m, 1H), 7.08-7.00 (m, 2H), 6.94-6.90 (dd, *J* = 7.8, 1.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ ppm: 157.22, 150.00, 145.84, 136.97, 133.12, 128.45, 128.15, 127.64, 125.84, 123.40, 121.39, 120.46, 116.93, 111.74; HRMS: *m/z* (ESI) calcd. for $C_{14}H_9OSBrNa$ [M+H]$^+$ 326.9455, found 326.9464; HRMS: *m/z* (ESI) calcd. for $C_{14}H_9OSBr$ [M] 305.95, 303.96, found 305.92, 303.82.

**2-(Naphthalen-1-ylthio)benzofuran (3i):** ^{1}H NMR (CDCl$_3$, 300 MHz) δ ppm: 7.87 (s, 1H), 7.80-7.75 (m, 3H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.49-7.32 (m, 7H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ ppm: 155.5, 146.3, 133.7, 129.1, 128.6, 127.8, 127.5, 127.0, 126.8, 126.6, 126.4, 123.7, 121.3, 111.7, 106.9; HRMS: *m/z* (ESI) calcd. for $C_{18}H_{12}OS$ [M+H]$^+$ 227.06; found 227.06.
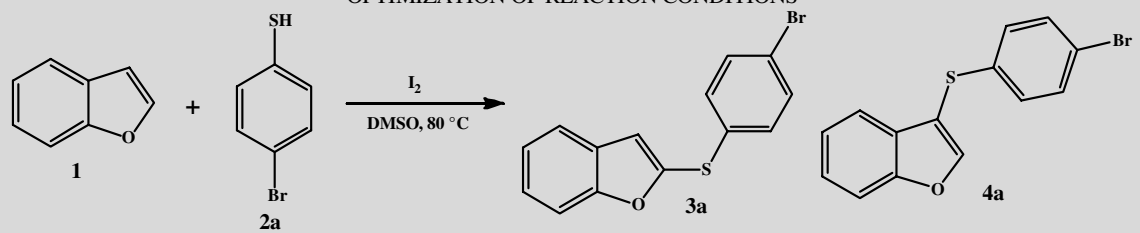
## RESULTS AND DISCUSSION

Initially, the reaction conditions were fine-tuned using benzofuran (**1**) and 4-bromo thiophenol (**2a**) as model substrates, as outlined in Table-1. The first sulfenylation process was performed using sodium iodide as catalyst in DMSO at 80 °C. The reaction gave a mixture of C-2/C-3 sulfenylated products (**3a** and **4a**) in 40% and 10% yield, respectively. Additionally, the influence of the catalyst was examined under the identical solvent and temperature conditions. It is noteworthy that molecular iodine was found to be the most optimal, resulting in 85% yield of the desired product (entry 1-6, Table-1). The significance of catalyst was illustrated by the fact that no reaction occurred in absence of any catalyst (entry 6). To enhance the product yield, the model reaction was carried out in different solvents such as DMF, ethanol and water, but, poor yields were observed (entry 7-9, Table-1). Additionally, adding catalyst loading up to 20 mol% had no effect on the reaction yield, suggesting that 5 mol% catalyst is the optimum amount for the intended procedure. It is important to highlight that temperature had a substantial impact on the reaction, since lower temperatures resulted in reduced yields of the desired products. After optimization, the standard conditions were found as benzofuran (**1a**) (0.2 mmol), 4-bromobenzenethiol (**2b**) (0.24 mmol), I$_2$ (5 mol%), DMSO (2 mL) at 80 °C in air.

Subsequently, we investigated the scope of reaction using variously substituted thiophenols adhering the optimized conditions. The electronic character of the substituents on the thiophenol ring had a discernible effect on product yield. In contrast to thiophenols with electron-donating substituents (**3e**, 80%), reactions with thiophenols containing electron-withdrawing groups (**3a**, 85% & **3b**, 84%) gave a greater yield of corresponding products. Conversely, strong electron-withdrawing groups such as *p*-NO$_2$ provided diminished product yield. It is interesting to observed that a large group like 1-naphthelenthiol was also found to be compatible and yielded 60% sulfenylated product. However, aliphatic mercaptans such as dodecane thiol and 2-aminothiophenol did not yield the expected product.

Various control experiments were conducted in order to better understand the reaction mechanism. Notably, the presence

**TABLE-1**
**OPTIMIZATION OF REACTION CONDITIONS**



| Entry | Catalyst | Solvent | Temperature (°C) | [b]Yield (%) |
|---|---|---|---|---|
| 1 | NaI | DMSO | 80 | 40 |
| 2 | KI | DMSO | 80 | 45 |
| 3 | CuI | DMSO | 80 | 32 |
| 4 | I$_2$O$_5$ | DMSO | 80 | 20 |
| 5 | I$_2$ (5 mol%) | DMSO | 80 | 85 |
| 6 | None | DMSO | 80 | 0 |
| 7 | I$_2$ | DMF | 80 | 50 |
| 8 | I$_2$ | EtOH | 80 | Trace |
| 9 | I$_2$ | H$_2$O | 80 | 0 |
| 10 | I$_2$ (20 mol%) | DMSO | 80 | 85 |
| 11 | I$_2$ | DMSO | 50 | 30 |

Reaction conditions: Benzofuran (**1a**) (0.2 mmol), 4-bromobenzenethiol (**2b**) (0.24 mmol), catalyst (5 mol%), solvent (2 mL), reaction time (6-8 h) in air. [b]Isolated yield of C-2 functionalized product.

of any radical scavenger did not impede the reaction progress, hence eliminating the radical pathway of the reaction. Moreover, the reaction in nitrogen environment using conventional parameters, resulting in 82% yield of product, that disregards the participation of ambient oxygen in the reaction process. Under standard conditions, reaction using only 2 moles of benzene thiol (**2a**), gave the diphenyl disulfide in 98% yield, suggesting formation of disulfide intermediate during the course of reaction. In accordance to preliminary control experiments and literature reports, the mechanistic path of the reaction is represented in **Scheme-II**. Initially, thiol undergoes oxidation in the presence of DMSO, resulting in the formation of disulfides **4**. These disulfides then react with iodine to yield intermediate **A**, RSI. Additionally, intermediate **A** interacts with benzofuran ring, resulting in the formation of resonance stabilized carbocation intermediate **B**. Then, intermediate **B** converted into the end product **3a**, with the concurrent elimination of HI. After that the HI molecule undergoes interaction with DMSO to give intermediate **C**. Subsequently, intermediate **C** reacts with another molecule of HI, leading to the production of intermediate **D**. Finally, regeneration of molecular iodine along with DMS and water takes place *via* nucleophilic attack of iodide ion on intermediate **D**.

**Docking studies:** The cytokine and receptor family known as interleukin-1 (IL-1) is distinct in the field of immunology due to its similarity in roles with the Toll-like receptor (TLR) family. The primary relationship of the IL-1 family is with innate immunity. Compared to other families of cytokines, interleukin-1 members are more strongly linked to deleterious inflammation; nevertheless, they also promote the development of the immune system's nonspecific tolerance to infection and foreign antigen recognition. Interactions between IL-1R1 and the other nine members of the IL-1 receptor family include IL-1α, IL-1β and IL-1Ra. IL-1R3 or the IL-1R auxiliary protein, is a coreceptor that, along with IL-1α and IL-1β, forms a trimeric signaling complex. IL-1β is an important player in cancer progression and atherosclerosis pathogenesis [19].

The applicability of synthetic benzofuran derivatives as interleukin IL-1β antagonists is investigated using molecular docking studies. The protein sequence IL-1β (P01584) was fetched from RCSB PDB database. Docking studies are carried out using Autodock and interaction images are extracted from
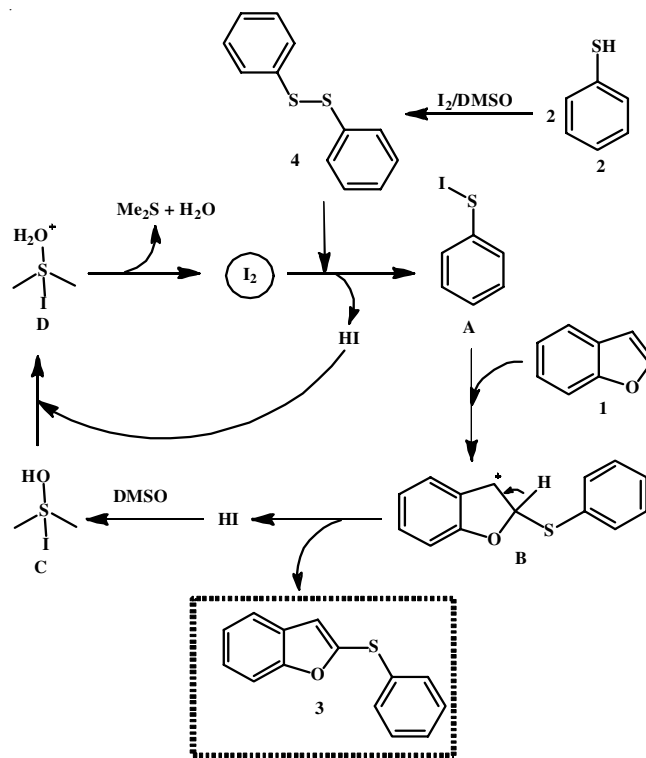


**Scheme-II:** Proposed mechanism

discovery studio programme. By using molecular docking studies, precise activity prediction and particular structure modelling may be accomplished. The relationship between inhibitors and the target protein's active site was investigated through the use of molecular docking experiments. Redocking the internal ligand into the protein's active site served as the initial step in validating the docking process. The docking procedure is validated when the root mean square deviation (RMSD) with the internal ligand is less than 2 Å. Lowest binding energy was obtained in range -6.62 to -8.0 Kcal/mol. Among all the molecules, **3i** was found to have lowest binding energy -8.0 Kcal/mol (Table-2). 2-D Ligand protein interactions and surface docking images of **3i** molecules are shown in Fig. 1.

**Conclusion**

An efficient and greener method was developed for the synthesis of C-2 thiolated benzofurans *via* cross dehydrogenative
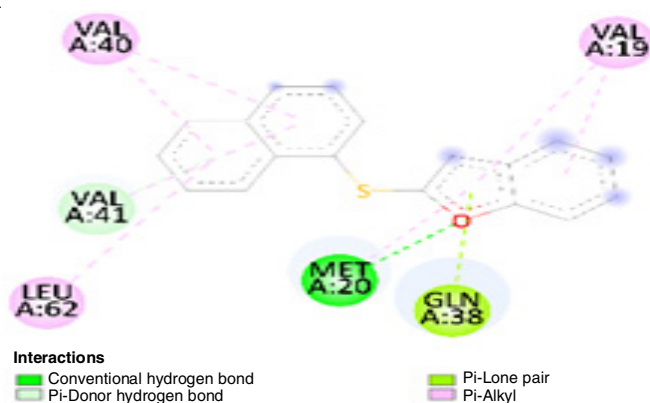


Fig. 1. Ligand-protein interaction of **3i** derivative with protein sequence IL-1β (P01584) images captured from docking software

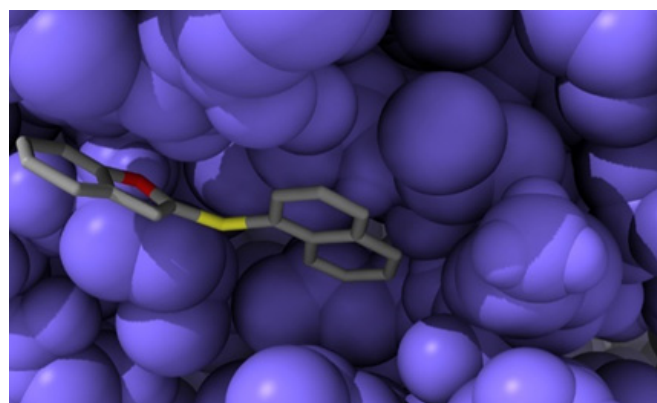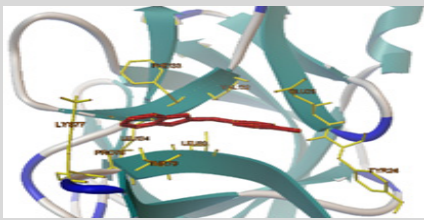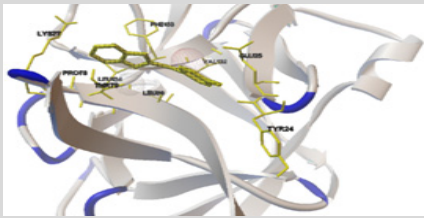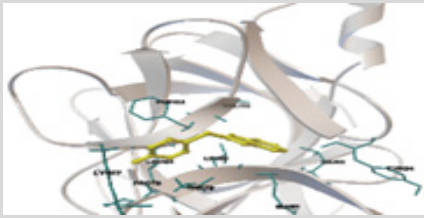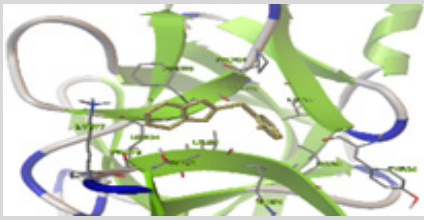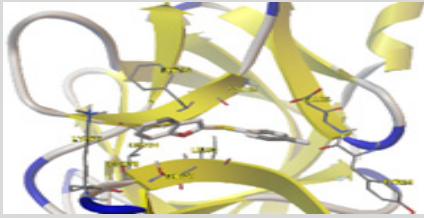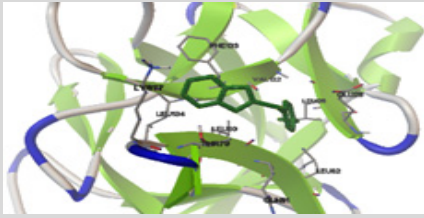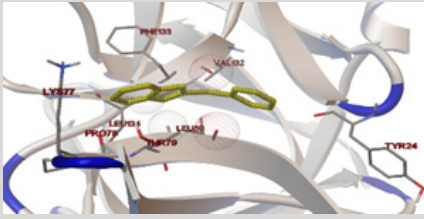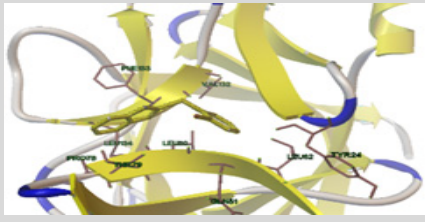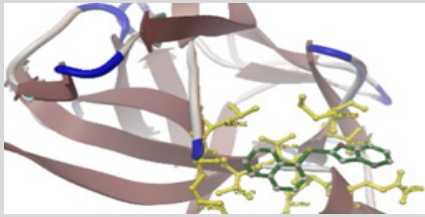| Ligand code | Binding energy (Kcal/mol) | Number of hydrogen bonds | Amino acids | 3-D interactions of ligand and protein |
|---|---|---|---|---|
| | | | **TABLE-2** | |
| | | | **DOCKING RESULTS AS INTERLEUKIN IL-1β ANTAGONIST** | |
| **3a** | -7.52 | 4 | Tyr24, Leu80, Glu25, Leu134, Thr79, Pro78, Lys77, Phe133, Val132, Glu25 |  |
| **3b** | -7.36 | 2 | Glu25, Leu134, Lys77, Tyr24, Val132, Thr79, Pro78 |  |
| **3c** | -6.19 | 1 | Pro78, Phe133, Gln81, Leu134, Lys77, Leu82 |  |
| **3d** | -6.62 | 1 | Leu80, Gln81, Leu134, Lys77, Phe133, Pro181 |  |
| **3e** | -7.2 | 3 | Glu25, Leu134, Thr79, Lys77, Pro78, Leu80, Tyr24, Val132 |  |
| **3f** | -7.02 | 2 | Leu28, Glu25, Val132, Lys77, Phe133, Glu25, Gln8, Leu134 |  |
| **3g** | -7.02 | 3 | Phe133, Leu134, Lys77, Thr24, Leu80, Pro78 |  |

| | | | | |
|---|---|---|---|---|
| **3h** | -7.3 | 1 | Pro78, Phe133, Val132, Leu134, Leu80, Thr79, Gln 81, Lue 82, Tyr24 |  |
| **3i** | -8.0 | 2 | Val41, Val19, Leu82, Met20, Gln99, Lys63 |  |

coupling in presence of $I_2$ as catalyst. Moderate to higher yields of thiolated benzofurans were obtained. The advantage of this approach lies in its straightforward synthesis and the absence of any potentially dangerous metal catalyst for the reaction. The molecular docking studies with Auto dock 2.0 revealed that these molecules can behave as interleukin IL-1β antagonist in biological system.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

## REFERENCES

1. Y.H. Miao, Y.H. Hu, J. Yang, T. Liu, J. Sun and X.J. Wang, *RSC Adv.*, **9**, 27510 (2019);
   https://doi.org/10.1039/C9RA04917G
2. K. Chand, Rajeshwari, A. Hiremathad, M. Singh, M.A. Santos and R.S. Keri, *Pharmacol. Rep.*, **69**, 281 (2017);
   https://doi.org/10.1016/j.pharep.2016.11.007
3. Z. Xu, S. Zhao, Z. Lv, L. Feng, Y. Wang, F. Zhang, L. Bai and J. Deng, *Eur. J. Med. Chem.*, **162**, 266 (2019);
   https://doi.org/10.1016/j.ejmech.2018.11.025
4. P.T. Thuy, N.V. Trang, D.X. Duc and N.T. Son, *Struct. Chem.*, **32**, 2271 (2021);
   https://doi.org/10.1007/s11224-021-01802-1
5. M. Thévenin, S. Thoret, P. Grellier and J. Dubois, *Bioorg. Med. Chem.*, **21**, 4885 (2013);
   https://doi.org/10.1016/j.bmc.2013.07.002
6. S. Rizzo, C. Rivière, L. Piazzi, A. Bisi, S. Gobbi, M. Bartolini, V. Andrisano, F. Morroni, A. Tarozzi, J.P. Monti and A. Rampa, *J. Med. Chem.*, **51**, 2883 (2008);
   https://doi.org/10.1021/jm8002747
7. Z.F. Hu, L.L. Chen, J. Qi, Y.H. Wang, H. Zhang and B.Y. Yu, *Fitoterapia*, **82**, 190 (2011);
   https://doi.org/10.1016/j.fitote.2010.09.002
8. A. Higashi, N. Kishikawa, K. Ohyama and N. Kuroda, *Tetrahedron Lett.*, **58**, 2774 (2017);
   https://doi.org/10.1016/j.tetlet.2017.06.005
9. Y. Wang, X. Hou, C. Liu, M. Lei, Q. Zhou, S. Hu and Z. Xu, *Inorg. Chem. Commun.*, **101**, 135 (2019);
   https://doi.org/10.1016/j.inoche.2019.01.026
10. P. Proksch and E. Rodriguez, *Phytochemistry*, **22**, 2335 (1983);
    https://doi.org/10.1016/0031-9422(83)80118-6
11. V. Sunitha, A.K. Kumar, B. Shankar, A.A. Kumar, T.M. Krishna, C.A. Lincoln and J. Pochampalli, *Russ. J. Gen. Chem.*, **87**, 322 (2017);
    https://doi.org/10.1134/S1070363217020281
12. Z. Liang, H. Xu, Y. Tian, M. Guo, X. Su and C. Guo, *Molecules*, **21**, 732 (2016);
    https://doi.org/10.3390/molecules21060732
13. R. Kenchappa, Y.D. Bodke, S. Telkar and M.A. Sindhe, *J. Chem. Biol.*, **10**, 11 (2017);
    https://doi.org/10.1007/s12154-016-0160-x
14. A. Hiremathad, K. Chand and R.S. Keri, *Chem. Biol. Drug Des.*, **92**, 1497 (2018);
    https://doi.org/10.1111/cbdd.13316
15. C. Wang, Y. Fan, Y. Yao, W. Chen, X. Cui, G. Zhu, W. Zhou and L. Tang, *ChemistrySelect*, **3**, 29 (2018);
    https://doi.org/10.1002/slct.201702142
16. J.L. Farmer, M. Pompeo, A.J. Lough and M.G. Organ, *Chem. Eur. J.*, **20**, 15790 (2014);
    https://doi.org/10.1002/chem.201404705
17. S. Vásquez-Céspedes, A. Ferry, L. Candish and F. Glorius, *Angew. Chem. Int. Ed.*, **54**, 5772 (2015);
    https://doi.org/10.1002/anie.201411997
18. Q. Zhen, D. Huang, Y. Shao, T. Cheng and J. Chen, *Org. Biomol. Chem.*, **16**, 9204 (2018);
    https://doi.org/10.1039/C8OB02680G
19. W. Widowati, K. Handono, M. Marlina, I.A. Sholihah, D.K. Jasaputra, T.L. Wargasetia, M. Subangkit, A. Faried, E. Girsang, I.N. Lister, C.N. Ginting, I.M. Nainggolan, R. Rizal, H. Kusuma and L. Chiuman, *Maced. J. Med. Sci.*, **10**, 65 (2022);
    https://doi.org/10.3889/oamjms.2022.7405