Computational and spectral studies of 3,3’-(propane-1,3-diyl)bis(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one)

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**ABSTRACT**

Detection and qualification of unknown impurities during commercial drug synthesis have been mandated by the regulatory authorities. 3,3’-(propane-1,3-diyl)bis(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one) in short IVA-9, is one such process-related impurity formed during the synthesis of cardiotonic drug Ivabradine. The structure and properties of this molecule have not been explored yet. A suggestive reaction route for the chance formation of IVA-9 during the commercial synthesis of parent drug molecule has been reported in this article. Further, the optimized geometry and vibrational studies have been computed using Gaussian 09. Experimental FTIR scan has also been performed and values show satisfactory consilience with the computational data. The frontier orbital energies and energy band gaps of the reaction fragments and products were computed. The evaluation of ADME parameters such as absorption, distribution, metabolism, and excretion are performed using SwissADME tool to assess the drug-likeness and medicinal chemistry friendliness. Six physiochemical parameters namely flexibility, lipophilicity, size, polarity, solubility and saturation and their critical limits are depicted using bioavailability radar of the programme to provide insights into pharmacokinetic properties such as human gastrointestinal absorption (HIA), blood-brain-barrier (BBB) permeability, total polar surface area (TPSA) and inhibitor action to important cytochromes etc.

**1. Introduction**

Impurity profiling is an important subset of the pharmacological drug development programme. Presence of impurity molecules in the pharmaceutical formulations might influence the therapeutic compliance and even jeopardize the safety and efficacy of drugs. Historically, impurity is any substance that impacts the percentage purity of the matter of interest like an active ingredient or drug material. However, these impurities do not necessarily affect the quality negatively all the time. Having said that, the purity of the active pharmaceutical ingredient (API) would be compromised, notwithstanding whether the impurity has superior pharmacological or toxicological property. Therefore, any foreign material-whether inert, toxic or pharmaceutically superior-must be thoroughly analyzed and accounted for [1]. 3,3’-(propane-1,3-diyl)bis(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one) (IVA-9) is an impurity produced during the commercial synthesis of cardiotonic drug Ivabradine. Ivabradine is a negative chronotropic drug which helps to lower heart rate without many adverse effects [2]. The natural pacemaker of the heart, also known as the sinoatrial node, undergoes spontaneous depolarization due to the recurring changes in its membrane potential [3]. Ivabradine functions by controlling the percolation of sodium-potassium ions through the hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels or the ‘f’ channels. This sodium-potassium current initiates the diastolic depolarization and hence is responsible for the pacemaker current. Ivabradine selectively blocks the ions flow through the HCN channels by physically binding on to these channels and this result in a reduced pacemaker current. A lowered pacemaker current ensures a reduced heart rate, dependent on the drug dosage [4]. Though sufficient information is available about the structure, properties [5, 6, 7], and estimation techniques [8, 9, 10, 11, 12, 13, 14, 15] of Ivabradine; there is little information available about its impurity molecule IVA-9 (Fig. 1a & 1b). The spectroscopic and volumetric estimation of the title molecule has been studied recently by the same authors [16]. At times, the exploratory studies of such molecules lead to the development of alternate drug molecules with better pharmacodynamics or help us to assess its toxicity impact. This has prompted the authors to undertake the structural and spectral studies of IVA-9 via experimental and computational approaches to assess the structure-property relationship. The primary screening of the physiochemical properties was also performed to assess and compare the
drug-likeness and toxicity effects vis-a-vis the parent drug. The authors are hopeful that these results might help in the future studies wherein IVA-9 could be explored as a potential drug molecule with good pharmacological properties and minimum toxicological impacts.

2. Materials and methods

3,3’-(propane-1,3-diyl)bis(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one) received as a gift sample was used as received. Shimadzu IRSpirt Fourier Transform Spectrophotometer was used for vibrational analysis of the sample between 4000-400 cm⁻¹ with a resolution of 2 cm⁻¹. Computational studies were performed using Gaussian 09 [17] and Gaussview 06 interface on VMware 8 core virtual CPU (Dell Power Edge R740 server). The optimized geometry, the geometrical parameters, and the vibrational spectrum were computed using Density Functional Theory (DFT) at basis set B3LYP/6-311g. SwissADME, a web-based tool is used to study the physiochemical aspects to assess the drug-likeness and pharmacokinetics of IV-9 [18]. The SwissADME web tool can be accessed freely via http://www.swissadme.ch.

3. Results

3.1. Synthetic route for ivabradine and chance formation of IVA-9 as an impurity

The routine synthesis of Ivabradine involves the reaction of 7,8-dimethoxy-1,3-dihydrobenzo[d]azepin-2-one (I) with dimethyl formamide to form 7,8-Dimethoxy-3-(3-chloropropyl)-1,3-dihydro-2H-3-benzazepin-2-one (II) which is then converted to its iodo-derivative (III). The compound III undergoes coupling with (IS)-4,5-Dimethoxy-1-[(methylamino)methyl]benzocyclobutane hydrochloride followed by selective hydrogenation to yield Ivabradine (Fig. 2) [19].

Though, IVA-9 was not a listed by-product of this reaction, the possibility of its chance formation as an impurity during commercial synthesis has been described by the following reaction route (Fig. 3).

3.2. Structural elucidation

The parent drug Ivabradine is a horse-shoe shaped molecule made up of two unsymmetrical bicyclic moieties (Fig. 4); first part containing a seven-member lactam unit whereas the latter has a cyclobutane part [5]. However, the impurity molecule is expected to be different from the parent molecule as it is formed by the dimerization of two lactam bearing segments connected via an alicyclic linkage. The structure is symmetric between two benzazepine units without the tertiary amino nitrogen. Computational modeling has emerged as a powerful tool to elucidate structural and spectral properties of unexplored molecules. The geometry optimization of the molecule was obtained by DFT modeling method using B3LYP/3-21g basis set and the same has been visualized with atom numbering in Fig. 5. The optimized molecule resembles a hat-shaped structure symmetric between two benzazepine units, unlike the horse-shoe shaped Ivabradine molecule. The benzene ring is distorted a bit as seen by the bond angles 118.9° and 119° at C1 and C6 positions respectively due to the presence of electron-releasing methoxy groups. Further, the methoxy substitution reduces the bond lengths between C1–C2 and C5–C6 to 1.39Å. The lactam chair is expectedly non-planar with bond angles of either 119° or 112° but with an increased bond angle of around 130° at N12. Further, there is a substantial reduction of bond length to 1.37 from 1.5Å between N12 and the beta carbon. There are considerable

![Fig. 1. (a): Ivabradine. (b): IVA-9.](image)

![Fig. 2. Literature method for the synthesis of Ivabradine [19].](image)
changes in bond angles at C10–N12–C11 (from 122° to 129.8°), at C10–N12–C13 (from 118.6° to 113.14°), at C11–N12–C13 (from 119.2° to 117°) and at N12–C13–C14 (from 112.2° to 115.4°) compared to Ivabradine molecule. These are presumably due to the replacement of cyclobutane segment by the repeat lactam unit here. The methoxy anisole groups on either side lie in more or less the same plane while the lactam units jut out at around 110° at halfway as shown by the dihedral angles. The apex of the hat made by the aliphatic linkage showed a bond angle of 116°. Out of the four methoxy groups, two (one each on either side) lie in the same plane as the benzene ring while other two (one each on either side) is out of the plane at a dihedral angle of 55° due to the possible torsional strains. The optimized structure visualizes that the lone pair on the lactam nitrogen delocalizes into the lactam ring. This has been corroborated by a short bond length of 1.37Å between N12 and C11. The list of significant dihedral angles is appended in below in Table 1.

The computed geometrical parameters such as bond lengths and bond angles were then compared with the experimentally obtained results. As no crystallographic data was available for IVA-9 in the literature, we have used the data pertaining to the lactam bearing segment of Ivabradine [21] for comparison. The results showed reasonable agreement between computed and experimental data (Table 2; Figs. 6 and 7).
| Sl. No. | Dihedral | Angle (°) | Sl. No. | Dihedral | Angle (°) |
|--------|----------|----------|--------|----------|----------|
| 1      | C6-C1-C2-C3 | -0.49 | 40 | C14-C15-N16-C29 | -62.34 |
| 2      | 032-C1-C2-C3 | 177.09 | 41 | C15-N16-C28-C26 | -176.58 |
| 3      | C2-C1-C6-C5 | -0.39 | 42 | C29-N16-C28-C26 | 7.60 |
| 4      | C2-C1-C6-C33 | 179.16 | 43 | C15-N16-C29-C27 | -178.42 |
| 5      | 032-C1-C2-C3 | -177.81 | 44 | C15-N16-C29-C30 | 3.16 |
| 6      | 032-C1-C6-C33 | 1.74 | 45 | C28-N16-C29-C27 | -2.70 |
| 7      | C2-C1-C32-C34 | 127.61 | 46 | C28-N16-C29-030 | 178.87 |
| 8      | C6-C1-C32-C34 | -54.93 | 47 | C22-C17-C18-C19 | 0.01 |
| 9      | C1-C2-C3-C4 | 0.95 | 48 | C27-C17-C18-C19 | -179.79 |
| 10     | C1-C2-C3-C9 | 179.15 | 49 | C18-C17-C22-C21 | 0.96 |
| 11     | C1-C3-C4-C5 | -0.53 | 50 | C18-C17-C22-C26 | -176.96 |
| 12     | C2-C3-C4-C8 | 177.83 | 51 | C27-C17-C22-C21 | -179.23 |
| 13     | C9-C3-C4-C5 | -178.83 | 52 | C27-C17-C22-C26 | 2.85 |
| 14     | C9-C3-C4-C8 | -0.47 | 53 | C18-C17-C22-C29 | 108.88 |
| 15     | C2-C3-C9-C10 | -108.03 | 54 | C22-C17-C27-C29 | -70.93 |
| 16     | C4-C3-C9-C10 | 70.20 | 55 | C17-C18-C19-C20 | -0.90 |
| 17     | C3-C4-C5-C6 | -0.34 | 56 | C17-C18-C19-043 | 178.71 |
| 18     | C8-C4-C5-C6 | -178.65 | 57 | C18-C19-C20-C21 | 0.80 |
| 19     | C3-C4-C8-C11 | -73.25 | 58 | C18-C19-040-C20 | 178.11 |
| 20     | C5-C4-C8-C11 | 105.07 | 59 | O43-C19-C20-C21 | -178.84 |
| 21     | C4-C5-C6-C1 | 0.80 | 60 | O43-C19-C20-C42 | -1.53 |
| 22     | C4-C5-C6-C33 | -178.71 | 61 | C18-C19-C43-C44 | -3.70 |
| 23     | C1-C6-C33-C38 | -177.67 | 62 | C20-C19-C43-C44 | 175.92 |
| 24     | C5-C6-C33-C38 | 1.85 | 63 | C19-C20-C21-C22 | 0.19 |
| 25     | C4-C8-C11-C12 | 54.54 | 64 | C19-C20-C21-C24 | 179.60 |
| 26     | C4-C8-C11-C25 | -123.58 | 65 | C42-C20-C21-C22 | -177.28 |
| 27     | C3-C9-C10-N12 | -48.79 | 66 | C42-C20-C21-C24 | 2.13 |
| 28     | C9-C10-N12-C11 | -14.74 | 67 | C19-C20-C42-C48 | 55.53 |
| 29     | C9-C10-N12-C13 | 616.68 | 68 | C28-C17-C27-C29 | -127.13 |
| 30     | C8-C11-N12-C10 | 11.06 | 69 | C20-C21-C22-C17 | -1.07 |
| 31     | C8-C11-N12-C13 | -170.53 | 70 | C20-C21-C22-C26 | 176.76 |
| 32     | C2-C15-N12-C10 | -170.89 | 71 | C24-C21-C22-C17 | 197.54 |
| 33     | C2-C15-N12-C13 | 7.52 | 72 | C24-C21-C22-C26 | -2.63 |
| 34     | C10-N12-C13-C14 | 61.87 | 73 | C17-C22-C26-C28 | 69.66 |
| 35     | C11-N12-C13-C14 | -116.80 | 74 | C21-C22-C26-C28 | -108.18 |
| 36     | C12-N12-C14-C15 | 78.64 | 75 | C22-C26-C28-N16 | -61.90 |
| 37     | C13-C14-C5-N16 | -51.41 | 76 | C17-C27-C29-N16 | 54.15 |
| 38     | C13-C14-C5-N16 | -51.41 | 77 | C17-C27-C29-030 | -127.38 |
| 39     | C14-C15-N16-C28 | 121.18 | | | |

Table 2

| Parameter      | Computed (Å) | Exptl (Ref) |
|----------------|--------------|-------------|
| Bond length    | C1-C2        | 1.39        | 1.37        |
|                | C1-C6        | 1.41        | 1.40        |
|                | C1-C32       | 1.39        | 1.38        |
|                | C2-C3        | 1.40        | 1.41        |
|                | C3-C4        | 1.40        | 1.39        |
|                | C3-C9        | 1.51        | 1.52        |
|                | C4-C5        | 1.40        | 1.41        |
|                | C4-C8        | 1.51        | 1.52        |
|                | C5-C9        | 1.39        | 1.38        |
|                | C6-033       | 1.54        | 1.52        |
|                | C8-C11       | 1.55        | 1.51        |
|                | C9-C10       | 1.49        | 1.46        |
|                | C10-N12      | 1.49        | 1.46        |
|                | C11-N12      | 1.37        | 1.35        |
|                | C11-025      | 1.26        | 1.23        |
|                | N12-C13      | 1.49        | 1.50        |
|                | C13-C14      | 1.54        | 1.53        |
|                | C14-C15      | 1.55        | 1.51        |
|                | C15-N16      | 1.49        | 1.50        |
Fig. 6. Bond lengths compared (IVA-9).

Fig. 7. Bond angles compared (IVA-9).

Fig. 8. (a): Experimental FTIR spectrum of IVA-9. (b): Computed IR Spectra of IVA-9 @ DFT-B3LYP/6-311g.
3.3. Vibrational studies

The solid state FTIR spectrum was recorded using Shimadzu IRSpirit Fourier Transform Spectrophotometer and the fundamental modes of vibrations were analyzed and interpreted. KBr pellet method was used for sample preparation and the scanning was done between 4000-400 cm⁻¹ with a resolution of 2 cm⁻¹. The vibrational frequencies were also computed using Gaussian09 with the optimized molecule geometry predicted by DFT at B3LYP/3-21g as the input. The optimized IVA-9 molecule has 69 atoms and 201 possible fundamental vibrations. The computed CH vibrational frequencies are scaled with a scaling factor of 0.966 for better agreement (See Fig. 8 (a) & (b); Table 3).

### Table 3

Vibrational frequencies and interpretations.

| Sl No | Wave number | Scaled wave No | Int. | Assignment | Experimental |
|-------|-------------|----------------|------|------------|--------------|
| 1     | 5201.511    | 3092.7         | 9.7  | Ar CH str Sym |              |
| 2     | 3197.202    | 3088.5         | 4.1  | Ar CH str Sym |              |
| 3     | 3190.851    | 3082.4         | 18.9 | Ar CH str Sym |              |
| 4     | 3188.837    | 3080.4         | 12.0 | Ar CH str Sym |              |
| 5     | 3155.395    | 3084.8         | 21.4 | Asymm CH str | Sym CH str (heterocyclic) |
| 6     | 3153.901    | 3086.7         | 23.5 | Asymm CH str | Sym CH str (heterocyclic) |
| 7     | 3149.812    | 3042.7         | 29.6 | Asymm CH str | Sym CH str (heterocyclic) |
| 8     | 3149.051    | 3042.0         | 29.6 | Asymm CH str | Sym CH str (heterocyclic) |
| 9     | 3116.002    | 3010.1         | 37.2 | Asymm CH str | Sym CH str (heterocyclic) |
| 10    | 3115.972    | 3010.0         | 65.1 | Asymm CH str | Sym CH str (heterocyclic) |
| 11    | 3111.785    | 3006.0         | 18.2 | Asymm CH str | Sym CH str (heterocyclic) |
| 12    | 3107.048    | 3001.4         | 14.3 | Asymm CH str | Sym CH str (heterocyclic) |
| 13    | 3099.331    | 2994.0         | 42.1 | Asymm CH str | Sym CH str (heterocyclic) |
| 14    | 3095.226    | 2990.0         | 28.4 | Asymm CH str | Sym CH str (heterocyclic) |
| 15    | 3083.884    | 2979.0         | 43.2 | Asymm CH str | Sym CH str (heterocyclic) |
| 16    | 3078.533    | 2973.9         | 48.8 | CH3 str (terminal) | Scis CH3 str (heterocyclic) |
| 17    | 3075.533    | 2971.0         | 52.6 | CH3 str (terminal) | Scis CH3 str (heterocyclic) |
| 18    | 3054.863    | 2951.0         | 73.4 | Asymm CH str | Sym CH str (heterocyclic) |
| 19    | 3054.102    | 2950.3         | 81.3 | Asymm CH str | Sym CH str (heterocyclic) |
| 20    | 3048.506    | 2944.9         | 47.1 | CH2 str (ali. link) | CH2 str (ali. link) |
| 21    | 3042.372    | 2938.9         | 12.4 | CH2 str (ali. link) | CH2 str (ali. link) |
| 22    | 3040.811    | 2937.4         | 51.3 | Sym CH2 str | Sym CH2 str (2910) |
| 23    | 3038.876    | 2935.6         | 11.0 | Sym CH3 str | Sym CH3 str (heterocyclic) |
| 24    | 3038.367    | 2935.1         | 15.4 | Sym CH3 str | Sym CH3 str (heterocyclic) |
| 25    | 3029.112    | 2926.1         | 33.1 | Sym CH3 str | Sym CH3 str (heterocyclic) |
| 26    | 3021.047    | 2918.3         | 91.6 | CH3 str (terminal) | CH3 str (terminal) |
| 27    | 3018.441    | 2915.8         | 102.8 | CH3 str (terminal) | CH3 str (terminal) |
| 28    | 3017.135    | 2914.6         | 37.7 | CH3 str (ali. link) | CH3 str (ali. link) |
| 29    | 3008.444    | 2906.2         | 62.6 | CH3 str (terminal) | CH3 str (terminal) |
| 30    | 3006.933    | 2904.7         | 62.6 | CH3 str (terminal) | CH3 str (terminal) |
| 31    | 2998.262    | 2896.3         | 46.0 | Sym CH2 str | Sym CH2 str (heterocyclic) |
| 32    | 2996.442    | 2894.6         | 53.1 | Sym CH2 str | Sym CH2 str (heterocyclic) |

(continued on next page)
| Sl No | Wave number | Scaled wave number | Int. Assignment | Experimental |
|-------|-------------|--------------------|----------------|--------------|
| 124  | 910.8218    | 879.6738           | 103.4          | CH in plane bend (heterocyclic) |
| 123  | 911.7235    | 880.5754           | 102.7          | CH in plane bend (heterocyclic) |
| 122  | 912.6252    | 889.4769           | 102.0          | CH in plane bend (heterocyclic) |
| 121  | 913.5269    | 898.3786           | 101.3          | CH in plane bend (heterocyclic) |
| 120  | 914.4285    | 907.2802           | 100.6          | CH in plane bend (heterocyclic) |
| 119  | 915.3301    | 916.1818           | 100.0          | CH in plane bend (heterocyclic) |
| 118  | 916.2317    | 925.0335           | 99.3           | CH in plane bend (heterocyclic) |
| 117  | 917.1333    | 933.8850           | 98.6           | CH in plane bend (heterocyclic) |
| 116  | 918.0350    | 942.6367           | 98.0           | CH in plane bend (heterocyclic) |
| 115  | 918.9367    | 951.1884           | 97.3           | CH in plane bend (heterocyclic) |
| 114  | 919.8384    | 960.3401           | 96.6           | CH in plane bend (heterocyclic) |
| 113  | 920.7400    | 969.4918           | 96.0           | CH in plane bend (heterocyclic) |
| 112  | 921.6417    | 978.6435           | 95.3           | CH in plane bend (heterocyclic) |
| 111  | 922.5434    | 987.7952           | 94.6           | CH in plane bend (heterocyclic) |
| 110  | 923.4451    | 996.9469           | 94.0           | CH in plane bend (heterocyclic) |
| 109  | 924.3468    | 1006.1086          | 93.3           | CH in plane bend (heterocyclic) |
| 108  | 925.2485    | 1015.2603          | 92.6           | CH in plane bend (heterocyclic) |
| 107  | 926.1502    | 1024.4119          | 92.0           | CH in plane bend (heterocyclic) |
| 106  | 927.0519    | 1033.5736          | 91.3           | CH in plane bend (heterocyclic) |
| 105  | 928.1536    | 1042.7353          | 90.6           | CH in plane bend (heterocyclic) |
| 104  | 929.2552    | 1051.8970          | 90.0           | CH in plane bend (heterocyclic) |
| 103  | 930.3569    | 1061.0587          | 89.3           | CH in plane bend (heterocyclic) |
| 102  | 931.4586    | 1070.2204          | 88.6           | CH in plane bend (heterocyclic) |
| 101  | 932.5603    | 1079.3821          | 88.0           | CH in plane bend (heterocyclic) |
| 100  | 933.6620    | 1088.5438          | 87.3           | CH in plane bend (heterocyclic) |
| 99   | 934.7637    | 1097.7055          | 86.6           | CH in plane bend (heterocyclic) |
| 98   | 935.8654    | 1106.8672          | 86.0           | CH in plane bend (heterocyclic) |
| 97   | 936.9671    | 1115.0289          | 85.3           | CH in plane bend (heterocyclic) |
| 96   | 937.0688    | 1124.1906          | 84.6           | CH in plane bend (heterocyclic) |
| 95   | 938.1705    | 1133.3523          | 84.0           | CH in plane bend (heterocyclic) |
| 94   | 939.2722    | 1142.5139          | 83.3           | CH in plane bend (heterocyclic) |
| 93   | 940.3739    | 1151.6756          | 82.6           | CH in plane bend (heterocyclic) |
| 92   | 941.4756    | 1160.8373          | 82.0           | CH in plane bend (heterocyclic) |
| 91   | 942.5773    | 1169.9990          | 81.3           | CH in plane bend (heterocyclic) |
| 90   | 943.6790    | 1179.1607          | 80.6           | CH in plane bend (heterocyclic) |
| 89   | 944.7807    | 1188.3224          | 80.0           | CH in plane bend (heterocyclic) |
| 88   | 945.8824    | 1197.4841          | 79.3           | CH in plane bend (heterocyclic) |
| 87   | 946.9841    | 1206.6458          | 78.6           | CH in plane bend (heterocyclic) |
| 86   | 947.0858    | 1215.8075          | 78.0           | CH in plane bend (heterocyclic) |
| 85   | 948.1875    | 1224.9692          | 77.3           | CH in plane bend (heterocyclic) |

and the computed peaks at 1807, 1796, 1783, 1772, 1765, 1767, 1769, 1761 and 1658 cm$^{-1}$ are assigned to this. The broad twin peak at 1635 cm$^{-1}$ in the FTIR ascribed to CO stretching. The corresponding in-plane bending is seen as weak bands at 955 and 925 cm$^{-1}$ whereas the out of plane bending is seen at 786 and 763 cm$^{-1}$ as strong bands. The characteristic peaks for methoxy groups are seen at around 1250 and 1050 cm$^{-1}$. The corresponding peaks are computed at 1289, 1268, 1281, 1268, 1257, 1250, 1250.4 and 1059, 1057, 1052, 1044, 1039, 1034, 1023, 1001, 999 cm$^{-1}$ respectively. FTIR peaks at 1355, 1313 & 1058, 1003 cm$^{-1}$ are indicative of this. The strong peak at 2841 cm$^{-1}$ in the experimental spectrum is typical of methylene asymmetric stretching in the heterocyclic ring. Some bands are visualized at 2934 and 2841 cm$^{-1}$ in theoretical calculation. The characteristic CN stretching
vibrations are visible at 1237, 1194 cm\(^{-1}\) and 1227, 1191 cm\(^{-1}\) in theoretical and experimental analysis respectively.

### 3.4. HOMO-LUMO energy gap

The energies of frontier orbitals are useful in assessing the chemical reactivity and thermodynamic stability of a system (See Fig. 9). In general, the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) indicate the electron-releasing and electron-gaining capacities respectively. The HOMO and LUMO energies of 7,8-dimethoxy-1,3-dihydrobenzo(d)azepin-2-one (I) & 7,8-Dimethoxy-3-(3-iodopropyl)-1,3-dihydro-2H-3-benzazepin-2-one (III), the addition product (IV) and IVA-9 are computed and presented in Table 4. A relatively larger HOMO-LUMO gap of 5.56 eV in IVA-9 is justifiable due to a relatively small aromatic system compared to the reagent compounds and intermediates. Due to this, IVA-9 shows higher kinetic and thermodynamic stability and less chemical reactivity. Further, the lack of conjugation renders the molecule colorless with fewer chances of electronic excitation in the visible range.

The energy gap of 5.56 eV in IVA-9 falls at around 225 nm in the ultraviolet region and the molecule is expected to show strong absorption at this wavelength. This has been cross-checked by performing UV-Visible scan via experimental (using Shimadzu UV-Vis spectrophotometer) and computational Time-Dependent DFT (TDDFT) methods and the results are given below (Fig. 10).

A relatively smaller electronic energy implies good stability of the impurity molecule compared to other reacting intermediates and the possibility of the molecule being carried over along with the active ingredient during commercial synthesis.

### 3.5. ADME studies

Safety and efficacy are vital aspects of the drug discovery process. It is important to know how the human body process and reacts to a drug system. A successful drug molecule must reach the target site in the adequate amount and remain there in its bioactive form till its intended biologic actions are performed. The evaluation of parameters such as absorption, distribution, metabolism, and excretion (ADME) are very important in this regard for a potential drug molecule. Drug development pipeline often produces a myriad of impurity and intermediate molecules with a potential drug-like character and toxicity effects. The onus is the investigator to spot the best molecule that could go on to become a potential medicine. SwissADME is a useful tool for this primary level of screening and helps in reducing pharmacokinetics-related failure during clinical trials at a later stage [25]. The output file contains a 2D chemical structure of the compound and bioavailability radar which gives a quick inference about the drug-likeness in a nutshell (Fig. 11). Six parameters namely flexibility, lipophilicity, size, polarity, solubility and saturation and their critical limits are depicted in the bioavailability radar (See Table 5). SwissADME also provides insights into other pharmacokinetic properties such as human gastrointestinal absorption (HIA), blood-brain-barrier (BBB) permeability, total polar surface area (TPSA) and inhibitor action to important cytochromes, etc.

By and large, IVA-9 shows similar physiochemical properties compared to Ivabradine. The cytochrome inhibitory actions are similar in most cases. It has a slightly higher total polar surface area (TPSA) due to the presence of extra polar carbonyl oxygen. This, in turn, results in a lower blood-brain-barrier (BBB) permeability. Overall, both molecules show comparable drug-likeness and medicinal chemistry friendliness indices.

### 4. Conclusions

The structural, spectral and physiochemical properties of the title molecule were studied. The lattice parameters and IR intensities computed showed reasonable concordance with the experimental results pertaining to the lactam bearing segment of Ivabradine molecule. The prospects of chance formation of IVA-9 impurity during the commercial manufacture of the parent drug were also discussed. A relatively larger HOMO-LUMO gap of 5.56 eV shows higher kinetic and thermodynamic stability and less chemical reactivity. The physiochemical properties of IVA-9 such as lipophilicity, water-solubility, polarity, and saturation are comparable to that of the drug molecule, Ivabradine. However, the bio-availability radar shows IVA-9 relatively more flexible than the parent.

### Table 4

| Compound     | HOMO (eV) | LUMO (eV) | ΔE (eV) | Dipole moment (D) | Electronic energy (eV) |
|--------------|-----------|-----------|---------|-------------------|------------------------|
| Compound I   | -5.83     | -1.06     | 4.77    | 3.12              | -27,170.70             |
| Compound III | -5.89     | -1.34     | 4.54    | 3.37              | -2,8,844.43            |
| Addition     | -4.91     | -2.86     | 2.05    | 2.89              | -43,499.50             |
| product IV   |           |           |         |                   |                        |
| IVA-9        | -5.40     | 0.16      | 5.56    | 1.39              | -43,572.97             |

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Fig. 9. HOMO-LUMO energy gap.

Fig. 10. UV-Visible spectrum of IVA-9.

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drug due to its symmetric structure. This could be a factor considering the fact that Ivabradine physically binds to the HCN channels to block the passage of ions. It would be useful to explore the possibility of using the impurity molecule for selective blocking in HCN channels due to the structural appropriateness. As a future scope, the article envisages the toxicity studies of the impurity when present along with the parent drug in pharmaceutical formulations.

Declarations

Author contribution statement

S Anil Kumar: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

B.L. Bhaskar: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Table 5

| Parameters                  | Ivabradine | IVA-9 |
|-----------------------------|------------|-------|
| No. of H bond acceptors     | 6          | 6     |
| No. of H bond donors        | 0          | 0     |
| Topological Polar Surface area, TPSA ([Å²]) | 60.5 | 77.5 |
| Lipophilicity, log P        | 3.4        | 2.99  |
| Water Solubility, log S     | -3.9       | -4.2  |
| GI absorption               | High       | High  |
| BBB permeant                | Yes        | No    |
| P-gp substrate              | Yes        | Yes   |
| CYP1A2 inhibitor            | No         | No    |
| CYP2C19 inhibitor           | No         | Yes   |
| CYP2C9 inhibitor            | No         | Yes   |
| CYP2D6 inhibitor            | Yes        | Yes   |
| CYP3A4 inhibitor            | Yes        | Yes   |
| Skin permeation, log Kp (Cm/S) | -7.37 | -7.31 |
| Drug likeness               | Yes        | Yes   |

Fig. 11. (a) Bio-availability radar-Ivabradine. (b): Bio-availability radar-IVA-9.

Additional information

No additional information is available for this paper.

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