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Theoretical Structural Analysis and IR Spectroscopic Differences of Constitutional Isomers of 4-Bromo-Di-tert-Butyl Aniline and Their Impact on Human Skin

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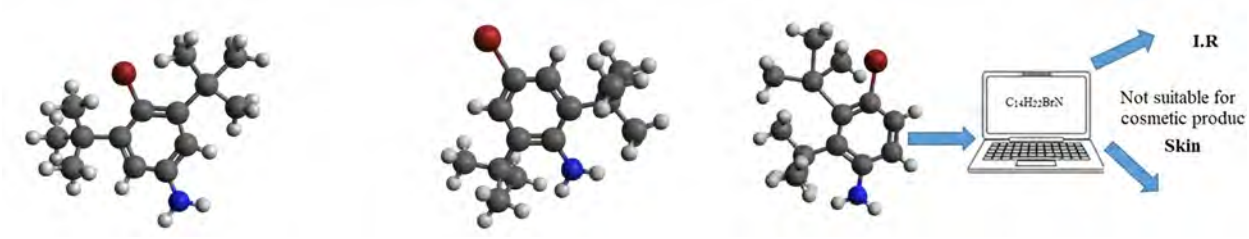
Abstract: This pilot study investigates the infrared (IR) spectroscopic differences among constitutional isomers of 4-bromo-di-tert-butyl aniline and evaluates their structural, vibrational, and dermatological properties using computational methods. Three isomers 4-bromo-3,5-di-tert-butyl aniline (Isomer A), 4-bromo-2,6-di-tert-butyl aniline (Isomer B), and 4-bromo-5,6-di-tert-butyl aniline (Isomer C) were analyzed employing density functional theory (DFT) at the B3LYP/6-31G* level. Geometry optimization and vibrational frequency calculations were performed using GAMESS, and theoretical IR spectra were simulated and compared.

The calculated IR spectra reveal complete overlap between Isomers A and B, indicating no significant vibrational differences despite their constitutional variation. In contrast, Isomer C exhibits minor variations in alkane C–H stretching and amine vibrational modes, attributed to the asymmetric positioning of tert-butyl substituents on the aromatic ring. All simulated spectra fall within the 400–3600 cm^{-1} range and show characteristic functional group vibrations consistent with aniline derivatives.

Quantitative structure–activity relationship (QSAR) modeling was employed to assess skin sensitization potential using multiple validated endpoints. The results indicate that all three isomers are predicted skin sensitizers, suggesting that these compounds may pose dermatological risks and are unsuitable for cosmetic applications. Overall, this study demonstrates the utility of combined DFT-based vibrational analysis and QSAR modeling for evaluating structural isomerism and predicting potential health hazards within the aniline family.

Key Words: Infrared spectroscopy, constitutional isomers, QSAR, skin sensitization, density functional theory (DFT)

CC1=CC(=CC(=C1Br)C)N
CC(C)(C)c1cc(Br)cc(c1N)C(C)(C)C



1. Introduction

The molecular formula of the compounds investigated in this study is $C_{14}H_{22}BrN$. Three constitutional isomers were considered: 4-bromo-3,5-di-tert-butyl aniline (Isomer A), 4-bromo-2,6-di-tert-butyl aniline (Isomer B), and 4-bromo-5,6-di-tert-butyl aniline (Isomer C). Infrared spectroscopy is a well-established analytical technique for identifying organic compounds and differentiating constitutional isomers that share the same molecular formula but differ in atomic connectivity [1]. The integration of experimental spectroscopy with computational analysis provides a robust framework for vibrational mode assignment and structural characterization.

Aniline derivatives constitute an important chemical family with extensive applications in environmental assessment, pharmaceuticals [2], polymer industries, agro-chemicals [3], textile dyes, paints, stationery products [4], and hair dyes [5]. The compound $C_{14}H_{22}BrN$ represents a moderately substituted member of this family. Substitution by tert-butyl groups can influence the intrinsic electronic and vibrational properties of aniline derivatives. Notably, aniline-based materials have demonstrated metallic-like behavior in conducting polymers [6,7], making them valuable in industrial applications. Furthermore, aniline derivatives serve as useful test systems for evaluating the accuracy of DFT methods in pharmaceutical and materials research [8]. Previous computational investigations have provided insight into reaction pathways and non-planar geometries of aniline derivatives using ab initio and DFT approaches [9,10]. Advances in computational chemistry and vibrational spectroscopy software have significantly enhanced the ability to predict molecular properties prior to experimental synthesis [11]. In materials science and chemical safety assessment, computational chemistry and toxicity prediction have become indispensable tools.

Skin sensitization remains a major concern for consumers and regulatory authorities, particularly for cosmetic ingredients [12]. Computational prediction of dermatological effects allows early-stage hazard screening while reducing reliance on animal testing. With continued development of computational chemistry platforms, predictive modeling has become an essential compl-ement to experimental investigations [13]. However, selecting an appropriate computational model for substituted aniline derivatives remains challenging. The present study addresses this issue by combining DFT-based vibrational analysis with QSAR-based dermatological assessment. Figure 1 features the

optimized forms of the three different isomers (A, B & C).

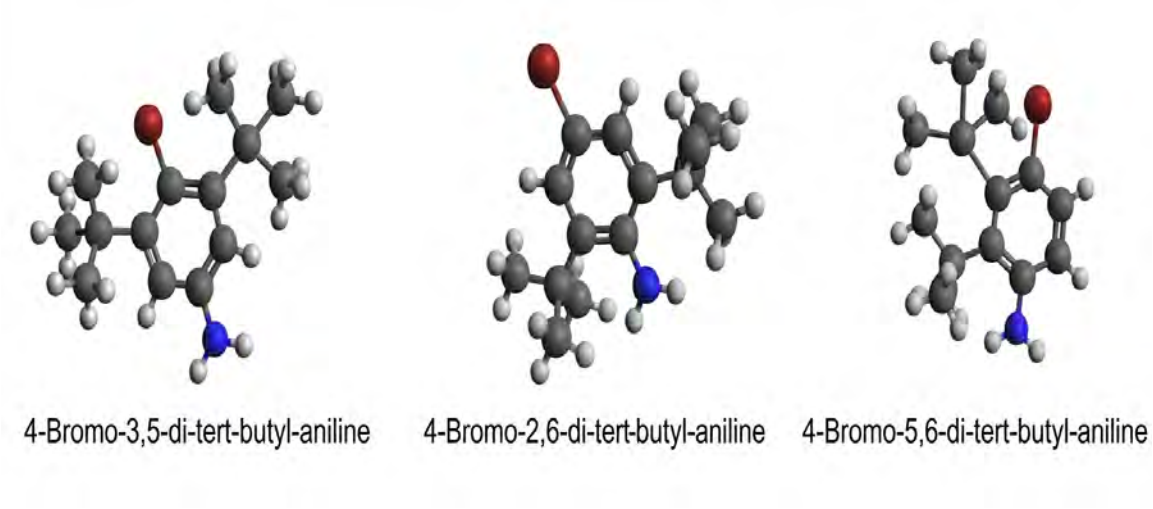


Fig 1. Arrangement of Isomers

Stereochemistry of Isomers

Each molecule contains an amino group attached to a single aromatic ring, with bromine substitution at the meta position. The aromatic ring comprises six carbon atoms, while two tert-butyl groups (4 + 4 carbon atoms) are attached at positions 3/2/5 and 5/6/6, giving a total of 14 carbon atoms. The molecules contain twenty-two hydrogen atoms, three double bonds, and no triple bonds, as illustrated in Figure 1.

2. Computational Method

Molecular structures were constructed using Avogadro 1.2 Molecular Editor [14]. Each isomer was geometrically optimized, and theoretical results were compared using the KnowItAll Informatics System. Vibrational frequency calculations and IR spectra simulations were performed using the GAMESS program [15]. Skin sensitization potential was evaluated using the LabMol Pred-Skin QSAR platform [16].

Parameter Use

IR spectra calculations were conducted using the B3LYP functional with the Pople 6-31G* basis set. It enhances the time of computation, giving better results. Parameters for electrostatic potential map calculations are same as the above parameters.

3. Computational Results

Isomer

Aniline molecular docking simulating base results show that isomers .All three isomers exhibited an identical molecular weight of 284.2 g/mol. Molecular weight provides very useful information such as viscosity. Higher molecular weight monomers require additional energy during formation processes. The molecular docking simulation tool is easily incorporated. Also, it more accurately models near to reality. Total number of atoms is 38.

I.R Theoretical Value

The spectrogram for IR value for 4-bromo-3,5-di-tert-butyl-tert aniline Isomer (A & B) lies in 0-3500 cm^{-1}. It is clearly interpreted from Figure 2. The following attachments are bonded with an aromatic ring:

- Alkanes: To confirm alkanes there are three types of atoms attachments, which are as follows:

$C-(CH_3)_3$, $R-CH_3$ &$CH-(CH_3)_2$.$C-(CH_3)_3$, C-H bending vibration, CH_3 asymmetric bending, 1470-1430 cm/1, CH_2 asymmetric bending, 1485-1445 cm/1, C-C medium stretching 1200cm/1. CH_3 asymmetric stretching, 3158 cm/1, CH_3 symmetric stretching, 3070 cm/1, which is slightly far, as shown in the spectrogram in Figures 2 and 3.

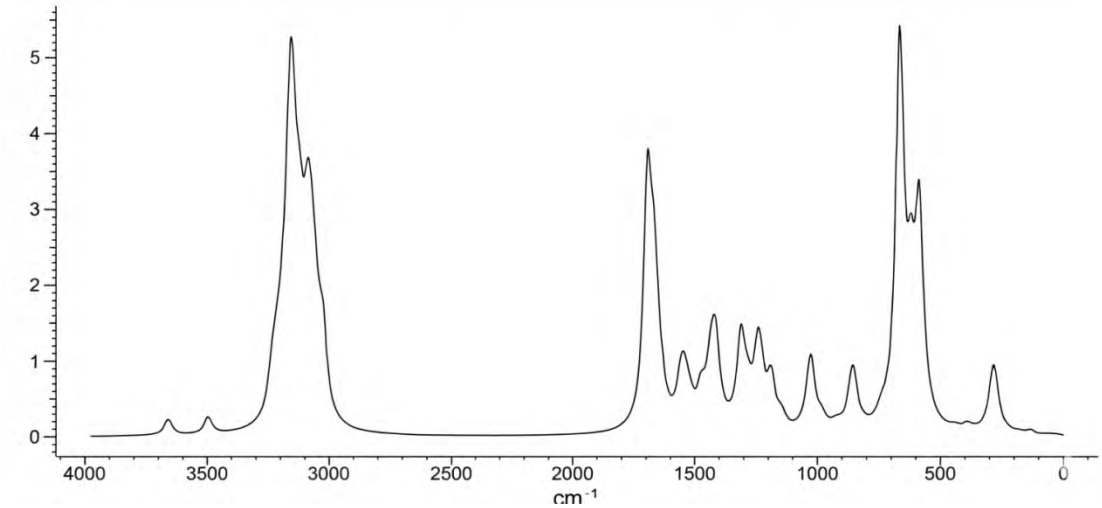


Fig 2. IR Spectrogram of 4-Bromo-3, 5-di-butyl-tert aniline (Isomer A)

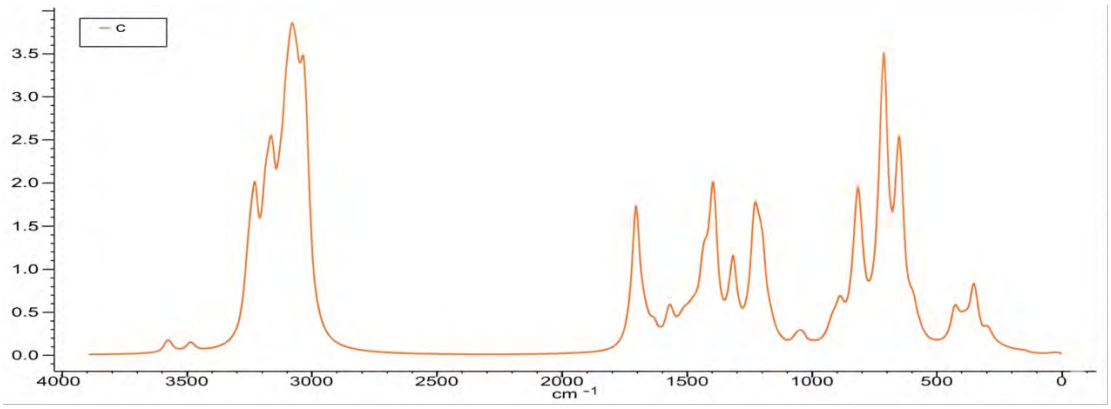


Fig 3. IR Spectrogram of 4-Bromo-5,6-di-tert-butyl aniline (Isomer C)

- Amine group: The presence of primary amine C-N medium stretching at 1304 cm^{-1}.NH_2, de-forming at 1629 cm/1, NH anti-symmetric, very minute peak at 3488 cm/1.
- Aromatic ring: The aromatic ring contains 1, 3, 4 & 5 substitute attachments, i.e., 1, 3, 4 & 5 carbons, as shown in Figure 1. C-H strong starching vibration peak at 3146 cm/1. Overtone of C-H wagging at 1692 cm-1. A minute peak of ring deformation at 851 cm-1. The presence of ring stretching at 17000 -1400cm^{-1}.
- Halogen group: The Isomer contains one halogen member, i.e., bromine, which is attached with carbon 4, and shows strong vibration at 664-528 cm^{-1}.

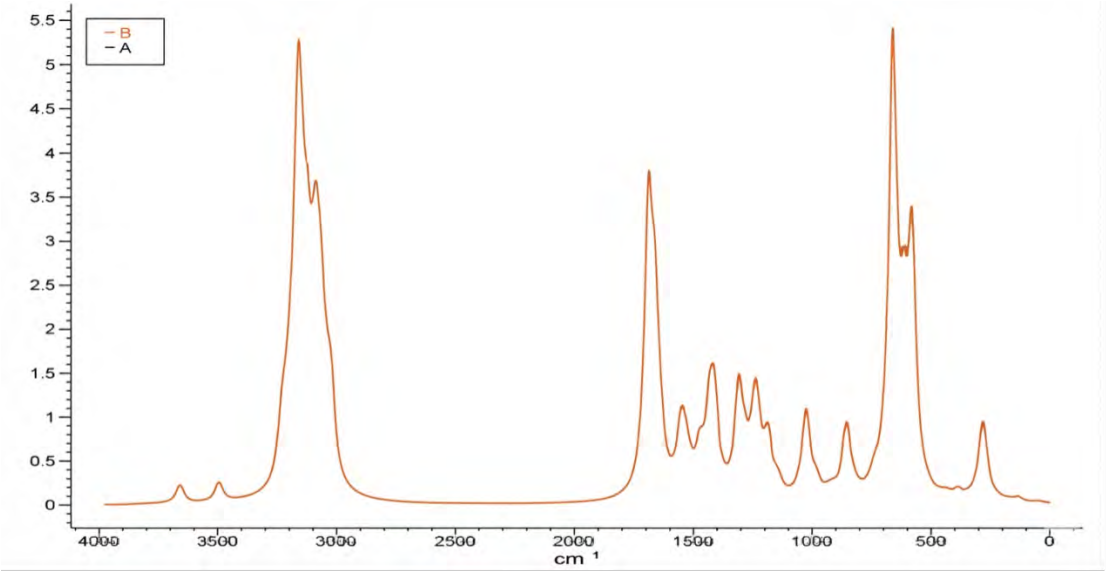


Fig 4. Compression Between Isomer (A) & Isomer (B) IR Spectrogram

From Figure 4, it is clear that both Isomers A & B are showing the same spectrogram (so there is no need to explain Isomer B separately).

From Figure 4, the IR spectra of Isomers A and B exhibit complete overlap, indicating no significant vibrational differences. It is further revealed that there is no difference.

Ergo, for determination of IR frequency, it is hard to differentiate the results.

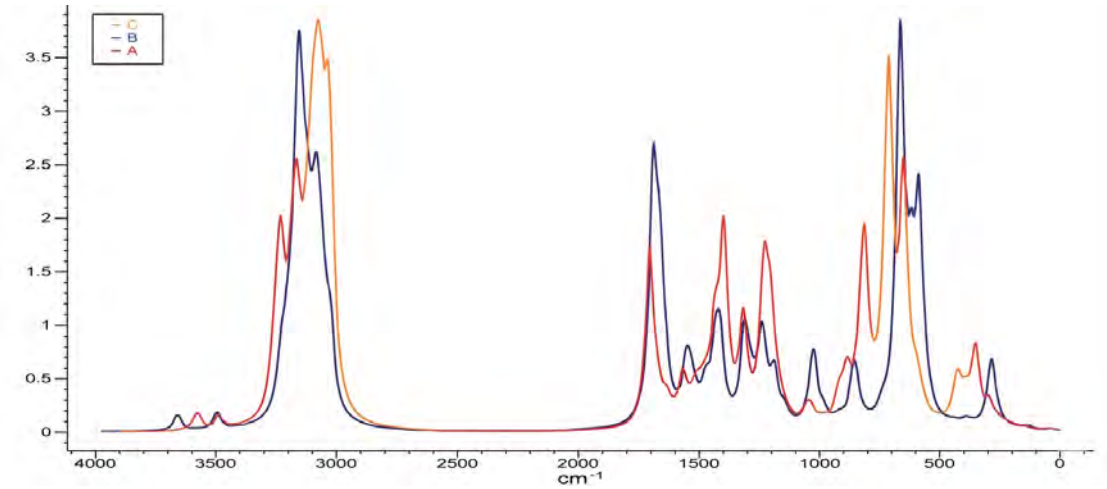


Fig 5. Compression Between Isomer (A), Isomer (B) & Isomer (C) IR Spectrogram

Theoretical NMR Analysis

From Figure 5, it is clear to see that the alkane C-H medium antisymmetric 1400 cm/1 intensity; the other alkane C-H symmetric intensity of Isomer C is also slightly high. The alkane CH symmetric at 3090 cm/1 high peak means strong vibration. These are due to the attachment of butyl atoms at one side. While the vibration of amine groups also slightly fluctuates, as shown in the spectrogram in Figure 5, small antisymmetric vibration of NH 3450 cm/1 are due to antisymmetric movement of hydrogen atoms that are attached with a nitrogen atom.

Theoretical NMR Analysis

Theoretical NMR chemical shift calculations were performed to evaluate the proton and carbon environments of the three constitutional isomers. The predicted ^{1}H NMR chemical shift values are presented in Table 2, while the corresponding ^{13}C NMR values are summarized in Table 3. Variations in the chemical shifts are primarily attributed to differences in substitution positions of tert-butyl groups on the aromatic ring, which influence local electronic environments.

Electrostatic Potential Map

In chemistry, electrostatic potential is a classical and fundamental concept. Many observables of molecules, such as dipole moments, chemical shift, and electromagnetic

spectra, can be correlated to atomic charges in the molecule, and many structure-property theories of molecules are based on the idea of atomic charges. The role of electrostatic potential in chemistry is a well-known [17] well-established concept in chemistry.

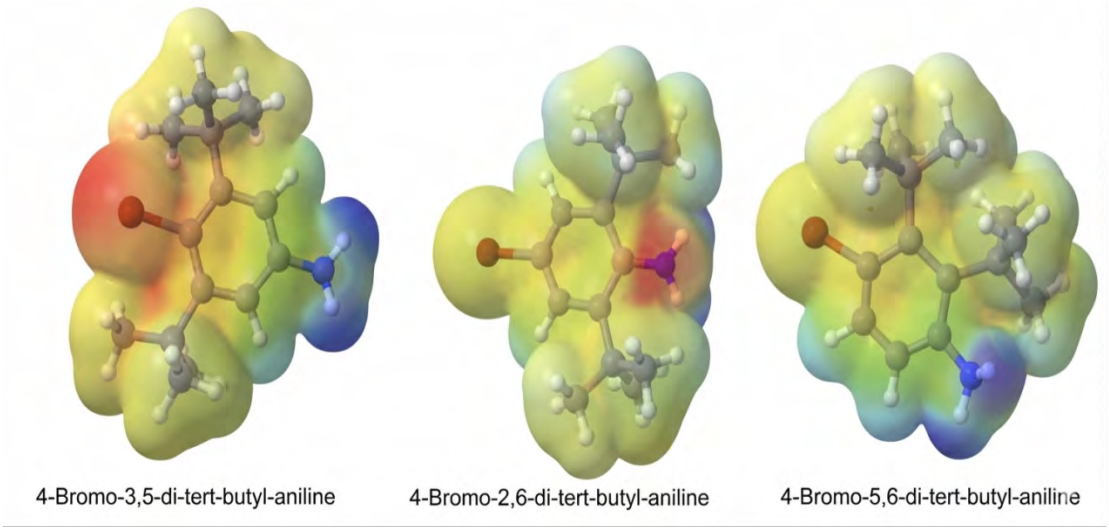


Fig 6. The Electrostatic Potential of Isomers

From Figure 6, it is clear to see that the charges of Isomer C are completely shifted towards one side.

Dermatological evaluation

"Is this organic isomer safe for human use?" is a fundamental question that arises before development and regulation of any cosmetics chemical, and evaluation of its toxicity impact on human skin [18,19]. With advancements in science, the practice of testing chemicals on animals is no longer needed, and the sale of cosmetics products tested on animals is also banned in developing countries.

Tables 1-3 show that the above-mentioned three isomers of aniline are skin sensitizers. This evidence proves that with human skin contact, they can lead to sensitization. These cause problems like damage to the immune system, interference with hormones, and may pose potential long-term health risks, subject to further experimental validation. Patho-mechanisms of the allergic response is a complex mechanism, although all the findings need confirmation in humans. Contact allergy is the result of the activation of both innate and adaptive immunity in response to haptens [20]. Cosmetics products directly used by humans may be released into the environment as an indirect consequence of their use [21].

Table 1. QSAR Models Based Skin Response Results

Test name	Isomer A Probability	Isomer B Probability	Isomer C Probability
1. Human skin	70%	70%	70%
2. Murine local lymph node assay	50%	60%	50%
3. Human cell line activation test	90%	90%	90%
4. Keratino Sens	80%	80%	90%

- Each prediction was performed in triplicate to ensure reliability and reproducibility of the QSAR model outputs.

Table 2. NMR H^1

Isomer A No. of H atoms	PPM	Isomer B No. of H atoms	PPM	Isomer C No. of H atoms	PPM
23,24	6.48	17,18	7.18	17	7.13
17-37	1.41	21-38	1.34	18	6.27
				30-38	1.41
	**********			21-29	1.35

Table 3. NMR 13 C

Isomer A No. of C atoms	PPM	Isomer B No. of C atoms	PPM No. of C atoms	Isomer C No. of C atoms	PPM
3,5	150	1	148	1,3	145
1	140	2,6	137	2	141
2,6	116	3,5	127	5	134
11-16	30.2	4	113	6	118
4	117	9,16	35	4	116
9,10	35.2	10-15	30	13	39
				12	36
	**********			9-15	30

4. Conclusion

The present computational study provides a systematic vibrational and dermatological assessment of three constitutional isomers of 4-bromo-di-tert-butyl aniline using density functional theory and QSAR-based modeling. The IR spectroscopic analysis demonstrates that Isomers A and B exhibit complete spectral overlap, indicating that constitutional variation at these substitution positions does not produce distinguishable vibrational differences. In contrast, Isomer C shows minor variations in alkane C–H stretching and amine vibrational modes, which can be attributed to the asymmetric placement of tert-butyl substituents on the aromatic ring.

Although the applied DFT methodology successfully reproduces key vibrational features of the aniline derivatives, the results also highlight the inherent limitations of purely theoretical approaches in fully resolving subtle isomeric differences in IR spectroscopy. Nevertheless, the combined use of vibrational analysis and electrostatic potential mapping provides valuable insight into substitution-dependent electronic effects within the aniline framework.

QSAR-based dermatological evaluation predicts that all three isomers possess skin-sensitizing potential. These findings suggest that, despite minor structural and vibrational differences, the constitutional isomerism examined here does not significantly alter the predicted dermatological risk profile. Accordingly, the studied compounds appear unsuitable for cosmetic applications, subject to further experimental validation. Overall, this work emphasizes the usefulness of integrated DFT and QSAR methodologies for evaluating structural isomerism, vibrational behavior, and potential health hazards of aniline derivatives. The approach presented here may serve as a supportive framework for preliminary hazard screening and for guiding regulatory considerations related to cosmetic and consumer-use chemicals.

5. Supplementary Data

Meta data associated with the current study also obtain from corresponding author on request.

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