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Novel bexarotene esters - synthesis and spectroscopic characterization

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Abstract. Bexarotene (Bex), a selective retinoid X receptor (RXR) agonist with established anticancer activity, is clinically constrained by poor aqueous solubility and unfavorable pharmacokinetics. This study aims to explore structural modification through the synthesis of Bex ester derivatives in order to improve physicochemical stability and expand its pharmaceutical applicability. Conventional esterification of Bex with thionyl chloride ($SOCl_2$) produces numerous by-products, which complicates purification and reduces yield. To overcome these challenges, an alternative and optimized synthetic route is applied, utilizing oxalyl chloride in primary alcohol media to generate four Bex esters: methyl (E1) and ethyl (E2), which are previously reported compounds, and two novel derivatives, propyl (E3) and butyl (E4). Reaction progression and purity are monitored by thin-layer chromatography (TLC), while the final products are isolated under controlled vacuum evaporation conditions. Structural confirmation and spectral profiling are performed using attenuated total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR) and ultraviolet-visible (UV-Vis) spectroscopy. The IR spectra reveal characteristic carbonyl signals near 1717 cm^{-1}, confirming ester bond formation, while UV-Vis measurements demonstrate preserved electronic transitions of Bex with absorption maxima around 204 and 262–264 nm. A validated UV-Vis method for quantitative determination of Bex shows excellent linearity ($R^2 = 0.9976$), precision (RSD < 0.64%), and sensitivity (LOD = 0.3 μg/mL). The synthesized esters display distinct solubility profiles and yields up to 81.5%, highlighting the relevance of this approach as a cleaner and more efficient alternative to conventional routes. These results establish a versatile synthetic platform and open avenues for future studies focused on advanced Bex derivatives, prodrug design, and improved drug delivery strategies.

***Keywords*:** bexarotene esters; TLC; spectroscopy; qualitative analysis; quantitative determination.

1. Introduction

Bexarotene (Bex), a synthetic retinoid, has garnered considerable attention in pharmaceutical research owing to its promising therapeutic applications, particularly in the treatment of various cancers and dermatological disorders [1–6]. Acting as a selective agonist of retinoid X receptors (RXRs), Bex modulates gene expression and influences key cellular processes such as proliferation, differentiation, and apoptosis [7-9]. Despite its favorable pharmacological profile, the clinical potential of Bex remains limited due to low aqueous solubility and rapid metabolic clearance, which compromise both its bioavailability and therapeutic efficacy [10].

Structural modification has emerged as an effective strategy to enhance the physicochemical and pharmacokinetic properties of bioactive molecules. Among these approaches, esterification is particularly attractive, as it allows tuning of lipophilicity and solubility, and in some cases enables prodrug behavior through enzymatic hydrolysis *in vivo* [11, 12]. Bex ester derivatives have the potential not only to improve these parameters but also to serve as intermediates in the design of advanced drug delivery systems.

Efficient reaction monitoring and structural characterization are crucial for the synthesis of such derivatives. Thin-layer chromatography (TLC) is widely recognized as a rapid and cost-effective tool for tracking reaction progress and verifying compound purity [13]. Complementary spectroscopic techniques, such as infrared (IR) and ultraviolet-visible (UV-Vis) spectroscopy, provide essential insights into molecular structure and electronic transitions, facilitating confirmation of ester formation and the evaluation of physicochemical modifications [14, 15].

The aim of the present study is to synthesize and comprehensively characterize a series of Bex esters - methyl (E1), ethyl (E2), propyl (E3), and butyl (E4) - using a refined esterification approach, combined with chromatographic and spectroscopic analyses, to establish a foundation for improved pharmaceutical formulations and future RXR-targeted therapies.

2. Experimental

2.1. Materials and reagents

Bexarotene (Free acid, Fluorochem); methyl alcohol (99.99 %, HPLC grade, Fisher Chemical); ethyl alcohol (≥ 99.8%, Analytical reagent grade, Fischer Chemical); 1-propanol (≥ 99% (GC), purum, Sigma-Aldrich); 1-butanol (≥ 99.5% (GC), Sigma-Aldrich); oxalyl chloride (98%, Sigma-Aldrich); thionyl chloride (99.5+%, Sigma-Aldrich); sulfuric acid (95-97%, Chem-Lab); butanol (anhydrous, 99.8% Sigma-Aldrich); ethyl acetate (≥ 99.8%, Fischer Chemical); hexane (99%

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HPLC, Lab-Scan); water (HPLC grade, Fisher Chemical).

2.2. Synthesis of bexarotene esters

Bexarotene (free acid, Fluorochem) and analytical grade alcohols (methanol, ethanol, 1-propanol, 1-butanol; Sigma-Aldrich/Fisher Chemical) are used as received. Ester derivatives (E1–E4) are prepared by dissolving 0.03 g (0.086 mmol) Bex in 30 mL of the respective alcohol under magnetic stirring (500 rpm) and gentle heating in a 100 mL one-neck round-bottom flask equipped with a reflux condenser, ensuring a homogeneous solution prior to reagent addition. Oxalyl chloride (0.4 mL, 4.66 mmol) is added dropwise under continuous stirring (500 rpm). The reaction mixtures were maintained under reflux at 40 °C for methanol and 60 °C for ethanol, 1-propanol, and 1-butanol, with total reaction times of 2 h for the first three alcohols and 3 h for 1-butanol, respectively. A few drops of concentrated sulfuric acid (H_2SO_4, 98%) are added as a catalyst and dehydrating agent to shift the equilibrium toward ester formation.

After completion of the reaction, the solvent was removed using a rotary vacuum evaporator (Heidolph Hei-VAP Expert) at 50 °C and 100 rpm. The pressure was adjusted according to the volatility of each alcohol, ranging from approximately 190 mbar for methanol to 16 mbar for 1-butanol, with evaporation times of 15–20 min to ensure complete solvent removal.

The progress and completion of the esterification reactions were monitored by thin-layer chromatography (TLC) on silica gel plates with UV_{254} indicator (ALUGRAM SIL G/UV_{254}, 0.20 mm). Several solvent systems were tested, and the best resolution between Bex and the ester products was achieved using hexane:ethyl acetate (1:1, v/v) as the mobile phase. Under these conditions, Bex exhibited an Rf value of 0.75, while the esters showed distinct and reproducible Rf values ranging from 0.55 (E1) to 0.72 (E4). The disappearance of the Bex spot and the presence of a single spot for each ester confirmed complete conversion and product purity. The chromatogram illustrates the clear separation and the systematic increase in Rf values with alkyl chain length, consistent with the expected polarity trend of the derivatives.

2.3. Characterization of bexarotene esters

Attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectroscopy is performed on the dried ester samples using a Thermo Scientific Nicolet iS10 FT-IR spectrometer (4000–600 cm^{-1}) with a Smart iTR attachment. Ultraviolet (UV) spectra are recorded for methanolic solutions of Bex and its esters in the 190–400 nm range using a T60UV spectrophotometer (PG Instruments Limited) and 1 cm quartz cells.

2.4. Spectrophotometric determination of Bex

A UV-Vis method was developed for the quantitative determination of Bex in methanol and was validated for linearity, precision, accuracy, and sensitivity following standard analytical protocols. Calibration curves are prepared using Bex solutions within the concentration range of 1.84–5.20 μg/mL.

3. Results and discussion

3.1. Synthesis of bexarotene esters

The synthesis of Bex esters is achieved through an optimized esterification strategy employing oxalyl chloride and primary alcohols (methanol, ethanol, 1-propanol, 1-butanol) in the presence of catalytic amounts of concentrated sulfuric acid (H_2SO_4, 98%). The acid acts as a dehydrating agent, driving the equilibrium toward ester formation, while oxalyl chloride activates the carboxylic group, ensuring efficient conversion and minimal by-product formation. Conventional esterification using thionyl chloride ($SOCl_2$) is known to produce multiple by-products and to complicate purification, which makes the oxalyl chloride/H_2SO_4 system a cleaner and more efficient alternative [16,17].

The choice of methanol, ethanol, 1-propanol, and 1-butanol is guided by their primary alcohol structure and systematic variation of alkyl chain length (C1–C4). This selection allows the evaluation of how increasing hydrophobicity influences the physical characteristics and potential pharmacokinetic behavior of the resulting esters. Short-chain derivatives, such as methyl and ethyl esters, are already known and may act as prodrugs with improved solubility [18], while the newly synthesized propyl and butyl esters introduce enhanced lipophilicity, which could improve membrane permeability and metabolic stability.

The overall synthetic pathway is presented in Figure 1, illustrating the conversion of Bex into its acid chloride intermediate, followed by esterification with the respective alcohols to yield E1–E4. This synthetic approach provides a robust platform for the generation of Bex derivatives with tailored lipophilicity and potential pharmaceutical relevance.

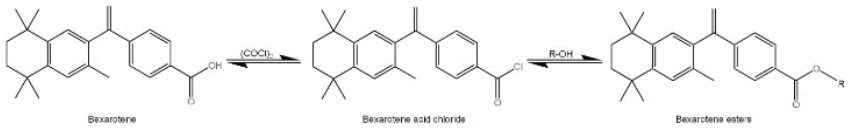


Figure 1. Synthetic pathway for the preparation of Bex esters (E1–E4).

The scheme from Fig. 1 illustrates the conversion of Bex into its acyl chloride intermediate using oxalyl chloride and catalytic H_2SO_4, followed by esterification with methanol, ethanol, 1-propanol, or 1-butanol to yield the corresponding methyl (E1), ethyl (E2), propyl (E3), and butyl (E4) esters.

During synthesis, distinct physical characteristics are observed. The methyl (E1) and ethyl (E2) esters form white crystalline solids, while propyl (E3) and butyl (E4) esters yield viscous, sticky substances with a yellow to light brown coloration. The appearance of white precipitates during the reactions with methanol

and ethanol suggests intermediate phase transitions linked to polarity differences between reactants and products. The synthesized esters were obtained in good yields, ranging from 64.2% for E3 to 81.5% for E4, with E1 and E2 showing intermediate values of 71.1% and 74.7%, respectively, which highlights the efficiency of the applied method.

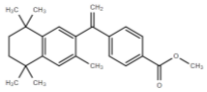
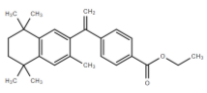
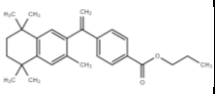
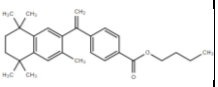
In the present work, the lowest yield was observed for the propyl derivative (E3, 64.2%). One possible explanation is that with increasing alkyl chain length the reaction equilibrium or solubility/precipitation behaviour becomes less favourable, leading to reduced isolated yield. Comparisons to the methyl and ethyl analogues, albeit from limited published data, support the notion that synthetic accessibility decreases with increasing alkyl chain length.

It is noteworthy that the methyl ester derivative of Bex has been reported in the literature mainly as an intermediate, either in multistep syntheses leading to Bex itself [19-21] or as a precursor for the preparation of various Bex analogues and derivatives [22]. In both cases, the methyl ester serves as a transient species and is not typically isolated or fully characterized, and no specific yield data are usually reported. For example, in a patent describing methods for preparing highly pure Bex, mono-alkyl esters (R = methyl, ethyl, *n*-propyl, etc.) are suggested as intermediates for subsequent activation and conversion, but no explicit yield data are provided for the methyl ester stage [23].

By contrast, an ethyl ester of Bex has been reported with a high yield of up to 95% under optimized conditions (e.g., using an acidic ionic-liquid catalyzed process) [24].

The physical properties of the esters, including solubility behavior, are summarized in Table 1.

Table 1. Physical characteristics and solubility of synthesized Bex esters.

Ester	Structure	Chemical name	Physical characteristics
E1		Methyl 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenil) ethenyl]benzoate	White crystalline substance, insoluble in water, soluble in methanol, ethanol, acetone and DMSO. Slightly soluble in hexane.
E2		Ethyl 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenil) ethenyl]benzoate	White crystalline substance, insoluble in water, soluble in methanol, ethanol, acetone and DMSO. Slightly soluble in hexane.
E3		Propyl 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenil) ethenyl]benzoate	White viscous substance, insoluble in water, soluble in methanol, ethanol, propanol and DMSO.
E4		Butyl 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenil) ethenyl]benzoate	Yellow-brown substance with increased viscosity, sticky, insoluble in water, soluble in methanol, ethanol, butanol and DMSO.

The completion of the esterification reactions and the purity of the obtained esters were confirmed by TLC, which showed single, well-defined spots for each compound and no residual Bex.

Although esterification is often considered primarily a prodrug strategy, preliminary computational data suggest that Bex esters retain intrinsic biological activity, albeit lower than that of the parent compound. This emphasizes the importance of their structural characterization and physicochemical evaluation. A promising direction for future studies is to explore esterification approaches that incorporate more polar functional groups, which could improve aqueous solubility while preserving or modulating biological activity. Such strategies, combined with detailed structure–activity relationship studies, may guide the rational development of Bex derivatives with enhanced pharmacokinetic and therapeutic profiles.

3.2. Infrared (IR) spectral analysis

The ATR-FTIR spectra of Bex and its ester derivatives (E1–E4) confirm the successful formation of ester functionalities and retention of the aromatic backbone. The spectrum of Bex, presented in Figure 3a, is characterized by a broad O–H stretching band in the 2500–3200 cm^{-1} region and a carbonyl C=O stretching band at 1697 cm^{-1}, both typical for carboxylic acids. In the spectra of the esters, shown in Figures 3b–3e, the disappearance of the O–H band confirms the loss of the free acid group, while the appearance of a sharper C=O band at approximately 1717 cm^{-1} indicates the formation of an ester functionality [14].

Characteristic C–O stretching vibrations are observed between 1180 and 1250 cm^{-1}, further confirming the conversion of the carboxylic group into ester groups. The aromatic C=C bands (1450–1600 cm^{-1}) and aliphatic $–CH_2$ /$–CH_3$ vibrations (2850–2960 cm^{-1}) remain unchanged, indicating that the esterification process does not alter the main Bex framework.

The shift of the carbonyl stretching band from 1697 cm^{-1} (Bex) to ~1717 cm^{-1} (esters) is consistent with the expected transformation of the carboxylic acid into ester derivatives. The ATR-FTIR spectra of E1–E4 are highly

similar, which can be attributed to their close structural resemblance - the only difference lies in the length of the alkyl chain in the ester moiety. As a result, only minor variations are observed in the fingerprint region, while the main absorption bands remain nearly identical. When combined with TLC data, these spectral findings suggest that the esterification occurs selectively at the carboxylic group and results in products of high purity.

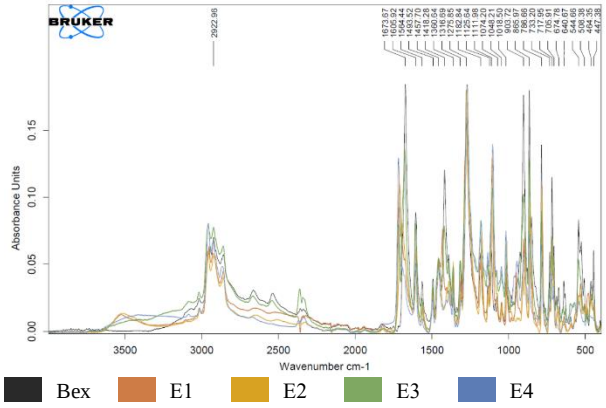


Figure 3. ATR-FTIR spectra of Bex and its ester derivatives (E1–E4), showing the disappearance of the O–H band and the shift of the C=O stretching vibration from 1697 to ~1717 cm^{-1}.

3.3. Ultraviolet (UV) spectral analysis

The UV-Vis spectra of Bex and its ester derivatives (E1–E4) were recorded in methanol at a concentration of 4.65 µg/mL. All compounds display two main absorption maxima: a strong band near 204 nm and a less intense but well-defined band around 262–264 nm. In the spectrum of Bex, these bands exhibit absorbance values of 0.798 and 0.245, respectively. Additionally, an absorption minimum appears at 232 nm with an absorbance of 0.184. The band at ~204 nm is typically attributed to high-energy σ→σ* and/or n→σ* transitions, whereas the band near 262–264 nm corresponds to π→π* transitions within the aromatic system of the Bex scaffold.

All ester derivatives show absorption patterns very similar to the parent compound, with only minor shifts in λ_{max} values (±1–2 nm) and slight variations in intensity. Consequently, only the spectrum of the parent compound is shown in Figure 4. The relative variation in absorbance intensity at the ~262 nm band for the esters remains within 5% (ranging from 0.812 to 0.892) compared to Bex, while the values for the ~204 nm peak range from 0.256 to 0.260. This indicates that the electronic transitions related to the conjugated system remain largely unaffected by esterification. Absorption minima are consistently observed around 236 nm for all esters, with absorbance values between 0.144 and 0.172.

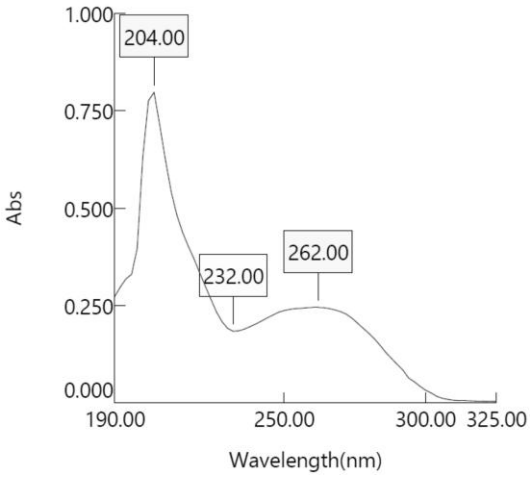


Figure 4. UV spectrum of Bex recorded in methanol, showing absorption maxima at 204 nm and 262 nm.

The presence and stability of the π→π* band near 262–264 nm across all esters confirm that the chromophoric system remains intact following esterification. The consistent UV-Vis profiles further support the conclusion that structural modifications are limited to the carboxylic acid group and do not affect the aromatic core. The minimal spectral shifts are expected, given that changes in the length of the alkyl ester moiety have negligible influence on the electronic transitions associated with the aromatic region.

3.4. Validation of the UV spectrophotometric method

The UV spectrophotometric method was validated for the quantitative determination of Bex in methanol, following standard analytical guidelines. The development and validation of this method were considered essential for the reliable monitoring of synthetic transformations and for supporting future investigations of Bex ester derivatives.

Although Bex exhibits a strong absorption maximum at approximately 204 nm, this region is typically associated with low selectivity and high background interference, particularly due to solvent absorption and instrumental noise. Therefore, the second absorption maximum near 262 nm - corresponding to a π→π* transition within the aromatic system - was selected as the analytical wavelength. This region offers improved specificity, reduced baseline fluctuation, and greater reproducibility, making it more suitable for quantitative analysis.

Methanol was selected as the solvent due to its low absorbance above 210 nm and its ability to dissolve both Bex and its ester derivatives without inducing hydrolysis or degradation.

Linearity. Excellent linearity was observed in the concentration range of 1.84–5.20 µg/mL, with a correlation coefficient (R^2) of 0.9976. The calibration curve followed the equation:

$$y = 174.66x - 0.0141$$

where $\boldsymbol{y}$ is the absorbance and $\boldsymbol{x}$ is the concentration (µg/mL). The calibration plot is shown in Figure 5.

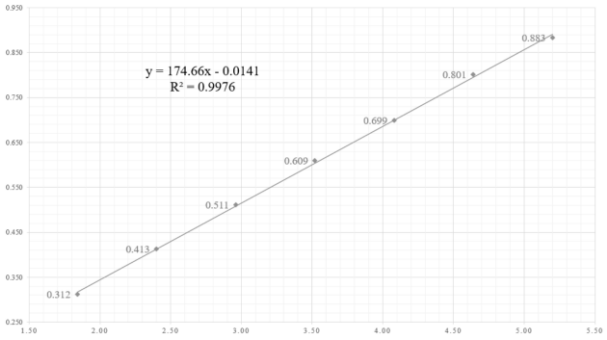


Figure 5. Calibration curve for Bex in methanol at 262 nm (λ_{max}), showing linearity in the range of 1.84–5.20 µg/mL (R^2 = 0.9976).

Precision (repeatability and reproducibility). Precision was evaluated by analyzing three concentration levels (1.84, 3.52, and 5.20 µg/mL) both within a single day (intra-day) and across consecutive days (inter-day). As shown in Table 1, the method demonstrates excellent repeatability and reproducibility, with all relative standard deviation (RSD) values below 0.65%.

Table 1. Evaluation of the repeatability and reproducibility of the UV-Vis spectral method.

Compound	*Concen-tration, µg/mL*	*Intraday analysis*		*Analysis within consecutive days*	
		SD	*RSD, %*	*SD*	*RSD, %*
Bexarotene	1.84	0.001483	0.496399	0.001924	0.642894
	3.52	0.002881	0.465123	0.001817	0.293757
	5.20	0.002280	0.258309	0.002864	0.324594

Accuracy. The method's accuracy was assessed through bias analysis at seven concentration levels within the linear range. As presented in Table 2, all bias values remained within ±2%, indicating high reliability of the method. Percent bias was calculated as:

$$Bias\ (\%) = \frac{C_{measured} - C_{nominal}}{C_{nominal}}\ x\ 100$$

Table 2. Evaluation of the accuracy of the UV-Vis spectral method.

Compound	**Concentration, µg/mL**	**Bias**	**Bias, %**
Bexarotene	1.84	0.03	1.63
	2.40	0.05	2.08
	2.96	0.05	1.69
	3.52	0.06	1.70
	4.08	0.01	0.25
	4.64	0.04	0.86
	5.20	0.06	1.15

Limit of Detection (LOD) and Limit of Quantification (LOQ). The LOD and LOQ, calculated using the standard deviation of the response and the slope of the calibration curve, were estimated to be 0.41 µg/mL and 1.36 µg/mL, respectively, indicating the method's sensitivity.

The validated method demonstrates excellent analytical performance in terms of linearity, precision, accuracy, and sensitivity. Despite being calibrated solely for Bex, the method shows promise for application to its ester derivatives, due to their conserved aromatic chromophores and similar UV-Vis spectral features. Quantification of such derivatives could be achieved following minor adjustments and appropriate calibration.

It should be noted, however, that the method is based on external calibration in a pure solvent system and does not account for potential matrix effects in more complex formulations or biological samples.

Overall, the method presents a rapid, reproducible, and cost-effective approach for the routine analysis, quality control, and synthetic monitoring of Bex and related ester compounds.

4. Conclusions

In this study, a synthetic strategy was developed for the preparation of a series of Bex esters via an acid chloride intermediate, employing a modified esterification protocol based on catalytic sulfuric acid under reflux conditions. The method proved to be operationally simple and efficient, avoiding the side reactions typically associated with conventional thionyl chloride activation. Among the four synthesized esters, two represent novel derivatives not previously reported in the literature.

Reaction monitoring by thin-layer chromatography confirmed the formation of distinct products for each alcohol used, and spectroscopic characterization through ATR-FTIR and UV-Vis analyses supported the successful structural transformation. The IR spectra of the esters displayed consistent ester carbonyl stretches, while the UV-Vis spectra showed minimal deviation from that of Bex, in line with their shared aromatic chromophores. A UV analytical method was developed and validated for the quantitative determination of Bex, demonstrating excellent linearity, precision, and accuracy within the tested range, and offering potential for extension to its ester derivatives.

The presented findings suggest that esterification represents a viable approach to structurally diversify the Bex scaffold while retaining key physicochemical characteristics. Such modifications may enable fine-tuning of solubility, lipophilicity, and potentially bioavailability. Although the synthesized esters are not designed as active agents *per se*, prior computational studies indicate that some of them may exhibit residual activity, suggesting their potential role as prodrug candidates.

Future work will focus on expanding the ester library through the incorporation of polar or functionally diverse alcohols, with the aim of modulating pharmacokinetic behavior. Furthermore, *in vitro* stability studies and enzymatic hydrolysis profiling will be necessary to evaluate their feasibility as prodrugs. Finally, additional spectroscopic and computational approaches will be explored to better predict and optimize the physicochemical properties of Bex derivatives.

Declaration of interest

The authors declare that they have no conflicts of interest.

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