

Microwave Accelerated Knoevenagel Condensation Approach: Synthesis, Characterization, ADMET and PASS Studies of Some Novel α , β - Unsaturated Dinitriles and Cyanoester.

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Abstract

Aromatic aldehydes performed a reaction with active methylene compounds, particularly malononitrile and ethyl cyanoacetate, to produce α , β -unsaturated dinitriles (**1-2**) as well as cyanoester (**3**). This was accomplished through a Knoevenagel condensation facilitated by microwave exposure and ammonium acetate in solvent free condition. The process was remarkably quick, completing in 30 seconds with yields of 97-99%. The resulting compounds were analyzed using FT-IR and ^1H NMR, and their physicochemical, pharmacological, and toxicity profiles were investigated through ADMET and PASS forecasts. Our research demonstrates a solvent-free microwave-assisted Knoevenagel method that produces high yields of α , β -unsaturated dinitriles and cyanoesters, and *in silico* ADMET and PASS studies highlighted their pharmacological potential and safety.

Keywords: Knoevenagel condensation; malononitrile; Cyanoester; Spectral characterization; ADMET and PASS prediction.

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সারমর্ম: এরোমেটিক অ্যালডিহাইডসমূহ সক্রিয় মিথিলিন যৌগের সাথে, বিশেষ করে ইথাইল সায়ানোএসিটেট এবং ম্যালোনোনাইট্রাইলের সাথে বিক্রিয়া করে α , β -অসম্পৃক্ত সায়ানোএস্টার এবং ডাইনাইট্রাইল তৈরি করে। এটি কোনও দ্রাবকের অনুপস্থিতিতে মাইক্রোওয়েভ এক্সপোজার এবং অ্যামোনিয়াম অ্যাসিটেটের মাধ্যমে সহজতর প্রক্রিয়ায় Knoevenagel ঘনীভবনের মাধ্যমে সম্পন্ন হয়েছিল। প্রক্রিয়াটি উল্লেখযোগ্যভাবে দ্রুত ছিল, 30 সেকেন্ডের মধ্যে সম্পন্ন হয়েছিল এবং যার ফলন ছিল 97-99%। ফলস্বরূপ যৌগগুলি FT-IR এবং ^1H NMR ব্যবহার করে বিশ্লেষণ করা হয়েছিল, ADMET এবং PASS পূর্বাভাসের মাধ্যমে তাদের ভৌত-রাসায়নিক, ফার্মাকোলজিকাল এবং বিষাক্ততার প্রোফাইলগুলি তদন্ত করা হয়েছিল। আমাদের গবেষণা একটি দ্রাবক-মুক্ত মাইক্রোওয়েভ-সহায়তাপ্রাপ্ত Knoevenagel পদ্ধতির প্রদর্শন করে যা α , β -অসম্পৃক্ত ডাইনাইট্রাইল এবং সায়ানোএস্টারের উচ্চ ফলন দেয় এবং *in silico* ADMET এবং PASS গবেষণায় তাদের ফার্মাকোলজিক্যাল সম্ভাবনা এবং সুরক্ষা তুলে ধরা হয়েছে।

1. Introduction

Carbon-carbon double bond formation is a crucial reaction in synthetic organic chemistry, notably through the Knoevenagel condensation between aldehydes and

active methylenes [1,2]. This reaction facilitates the formation of substituted alkenes and bioactive molecules, serving as a vital step in the synthesis of natural products [3]. Knoevenagel condensation is gaining prominence due to its diverse applications in cosmetics, perfumes, pharmaceuticals, and agrochemicals [4]. It primarily involves active methylene compounds such as malononitrile and ethyl cyanoacetates, typically executed with weak organic bases or Lewis's acids. However, traditional methods using hazardous solvents like benzene necessitate long heating periods and generate significant organic waste [5]. Alternative approaches, including ionic liquids, recyclable catalysts, and microwave activation, have been explored to improve efficiency and reduce environmental impact [6,7].

The Knoevenagel condensation is a crucial organic synthesis reaction that forms carbon-carbon double bonds by condensing aldehydes or ketones with active methylene compounds like malononitrile or cyanoesters [8,9]. It is essential for generating α , β -unsaturated dinitriles and cyanoesters, which are key intermediates in pharmaceuticals, agrochemicals, and functional materials. Traditionally done under mild conditions with basic or Lewis's acid catalysts, recent advancements now utilize microwave irradiation to enhance efficiency and sustainability [10]. Microwave (MW)-assisted Knoevenagel condensation significantly reduces reaction times, increases yields, and may allow for solvent-free methods, aligning with green chemistry principles by minimizing waste and energy consumption [11,12]. The microwave-accelerated Knoevenagel condensation is effective for a variety of aldehydes and active methylene compounds, producing α , β -unsaturated dinitriles and cyanoesters known for their antimicrobial, anticancer, antioxidant, and anti-inflammatory properties [13,14]. These compounds can act as electrophiles in Michael addition reactions and activate the NRF2 signaling pathway, important for cellular defense against oxidative stress. MW-assisted methods offer operational simplicity and environmental benefits, facilitating the rapid synthesis of diverse compound libraries for drug discovery and materials science [15,16]. As research progresses, new applications in drug discovery and green chemistry are expected to emerge from this technology. Microwave irradiation (MWI) has emerged as a widely utilized non-conventional energy source for activating reactions in organic chemistry, offering benefits such as shorter reaction times, cleaner products, and improved yields and selectivity [17,18]. The present work presents a rapid and green microwave-assisted Knoevenagel condensation conducted under solvent-free conditions, yielding α , β -unsaturated dinitriles and cyanoesters in excellent yields within seconds. This method is more efficient and simpler than previous approaches, emphasizing environmental sustainability. It also incorporates *in silico* ADMET and PASS analyses to evaluate pharmacological relevance and toxicity, making it valuable for medicinal chemistry.

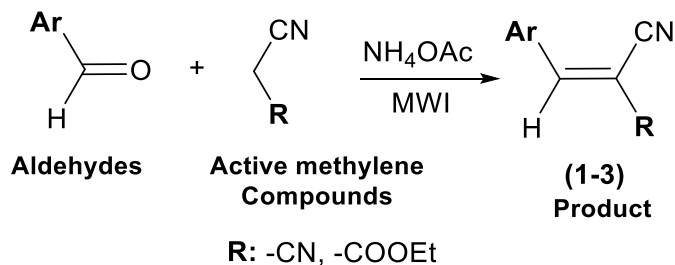
2. Methodology

2.1. Chemicals and materials

Malononitrile, ethyl cyanoacetate, aromatic aldehydes, ammonium acetate, and all solvents (e.g., methanol, ethanol, ethyl acetate, acetone and *n*-hexane) were obtained from standard commercial suppliers (e.g., Merck, Sigma-Aldrich, or equivalent) and were of analytical grade. All solvents were purified prior to use by distillation at their boiling points and mixture of *n*-hexane: ethyl acetate (6:1) were utilized. Coated TLC with silica gel 60, kieselguhr F₂₅₄ (thickness 0.02 cm F. MARACK, on aluminium plates were used for TLC). Ethanol and acetone were distilled during analysis. Melting points were determined using a Shimadzu DSC-60 apparatus. FTIR spectroscopy was conducted utilizing KBr matrix within the range of 4000-400 cm⁻¹ on a Shimadzu 8900. ¹H-NMR spectra were recorded using a Bruker Avance III HD 400 MHz spectrometer with solvents CDCl₃, CD₃OD, and DMSO-d₆, reporting chemical shifts in δ (ppm) referencing TMS. Reactions were carried out in a LG microwave oven (MB-3947C) with a maximum of 800 W at 2450 MHz. Thin layer chromatography was performed on Kieselgel GF254, using UV light for visualization.

2.2. General synthesis of α , β -unsaturated dinitriles and cyanoester.

The methodology for the synthesis of α , β -unsaturated dinitriles (**1-2**) and cyanoester (**3**) was employed the reaction of aromatic aldehydes (e.g., (4-octanyloxyphenylcarboxy)benzaldehyde, 4-hexadecanyloxybenzaldehyde, 4-octadecanyloxybenzaldehyde) with active methylene compounds (e.g., malononitrile and ethyl cyanoacetate) in the presence of a catalytic amount of NH₄OAc under microwave irradiations (**Scheme 1**) [9]. In microwave conditions, the rate of reaction occurs rapidly as a result the reaction times become shorter and yields are high with easy isolation of products. Thus, a mixture of aromatic aldehydes, active methylene compound and catalyst (NH₄OAc) were mixed in a flask. The mixture was subjected to microwave heating under the appropriate conditions setting in a domestic oven and then it allowed reaching to room temperature. The reaction mixture was treated with TLC (*n*-hexane: ethyl acetate, 6:1) for solidification and the solid product was separated by filtration and then the product was washed and dried. Suitable solvent or solvent mixtures (*n*-hexane: ethyl acetate 6:1) recrystallized the solid product to yield the dinitriles (**1-2**) and cyanoester (**3**) (**Table 2**).



Scheme 1 Synthesis of some novel α , β -unsaturated compounds (1-3) [9].

Table 1 Microwave assisted Knoevenagel condensation reaction between aromatic aldehydes and malononitrile/ethyl cyanoacetate (1-3).

Serial no.	Substrate	Reagent	Product	Watt/Time (Sec)	% of yield	Melting point (°C)
1				300W, 30 sec	97.55%	65-68
2				320W, 30 sec	98.64%	82-84
3				320W, 30 sec	99.10%	60-62

In our research, Microwave-assisted Knoevenagel condensation achieves higher yields due to rapid, uniform heating, enhanced reaction kinetics, minimal side reactions, improved catalyst performance, and favorable equilibrium conditions, resulting in efficient product formation with high purity within a shorter time.

2.3. Spectral data of synthesized compounds (1-3).

4-octadecanyloxybenzylidenemalononitrile (1).

IR (KBr) $\nu_{\max}$ (cm^{-1}): 3031.26 (str, C-H, Ar), 2224.02 (str, -CN), 1653 (str, C=C), 1581.70 (str, C=C, Ar), 1183.38 (C-O, str, ether).

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ_{H} (ppm): 7.93 (d, 2H, $J=8.8\text{Hz}$, Ar), 7.66 (1H, s, -CH=C), 7.02 (2H, d, $J=8.8\text{ Hz}$, Ar), 4.08 (t, 2H, $J=8\text{ Hz}$ -OCH₂-), 1.82 (m, 32H, (-CH₂)₁₆), 0.90 (t, 3H, $J=8\text{ Hz}$, CH₃-).

2-(4-(4-octanyloxyphenylcarboxy)benzylidene)malononitrile (2).

IR (KBr) $\nu_{\max}$ (cm^{-1}): 3011.98 (str, C-H, Ar), 2223.06 (str, -CN), 1738.90 (C=O, ester, str), 1699.36 (str, C=C), 1591.34 (str, C=C, Ar), 1166.02, 1056.07 (C-O, str, ether).

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ_{H} (ppm): 8.16 (d, 2H, $J=8.1\text{ Hz}$, Ar), 8.03 (d, 2H, $J=8.8\text{ Hz}$, Ar), 7.79 (s, 1H, CH=C), 7.46 (d, 2H, $J=8.8\text{ Hz}$, Ar) 7.02 (d, 2H, $J=8.8\text{ Hz}$, Ar), 4.07 (t, 2H, $J=6.4\text{ Hz}$, -OCH₂), 1.85 (m, 12H, (-CH₂)₆), 0.92 (t, 3H, $J=6.4\text{ Hz}$, -CH₃).

Ethyl 2-cyano-3-(4-hexadecanyloxyphenyl) acrylate (3).

IR (KBr) $\nu_{\max}$ (cm^{-1}): 3079.10 (str, C-H, Ar), 2218.23 (str, -CN), 1719.61 (str, C=O, ester), 1716.72 (str, C=C), 1586.52 (str, C=C, Ar), 1179.52, 1095.61 (C-O, str, ether).

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ_{H} (ppm): 8.1 (s, 1H, -CH=C), 8.02 (d, 2H, $J=8.8\text{ Hz}$, Ar), 7.00 (d, 2H, $J=8.8\text{Hz}$, Ar), 4.38 (q, 2H, $J=7.2\text{Hz}$, -OCH₂), 4.06 (t, 2H, $J=6.4\text{ Hz}$, -OCH₂), 1.43 (m, 28H, (-CH₂)₁₄), 1.34 (t, 3H, -CH₃), 0.92 (t, 3H, $J=6.4\text{ Hz}$, -CH₃).

3. Results and discussion

3.1. Characterization of the synthesized compounds (1-3).

All the microwave-assisted synthesized α , β -unsaturated compounds (**1-3**) were characterized by the modern spectral (FTIR, and $^1\text{H-NMR}$) data analysis. The advancement of all reactions was traced by TLC (*n*-hexane: ethyl acetate, 6:1). The yields were obtained as a crystal.

3.1.1. 4-octadecanyloxybenzylidenemalononitrile (1).

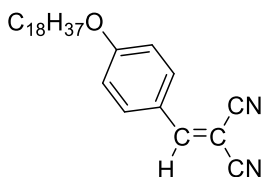


Figure 1 Chemical structure of 4-octadecanyloxybenzylidenemalononitrile (**1**).

The compound 4-octadecanyloxybenzylidenemalononitrile (**1**) in its IR spectrum showed an absorption stretching band at 3031.26 cm^{-1} indicating the presence of aromatic C-H bond. The absorption bands at 1653.07 cm^{-1} and 1581.70 cm^{-1} were assigned the presence of C=C (olefinic) and aromatic C=C bond respectively. The absorption stretching band at 2224.02 cm^{-1} is due to -CN bond. An absorption stretching band at 1183.38 cm^{-1} is due to the presence of C-O (ether) group.

Again, the compound 4-octadecanyloxybenzylidenemalononitrile (**1**) in its $^1\text{H-NMR}$ spectrum exhibited a one-proton singlet signal resonated at $\delta_{\text{H}} 7.66$ in the downfield region designated the presence of CH=C proton. The two two-proton doublet signals resonated at $\delta_{\text{H}} 7.93$ and $\delta_{\text{H}} 7.02$ with J value 8.8 Hz to aromatic H-2, H-6 and H-3, H-5 protons respectively. The spectrum showed a two-proton triplet signal resonated at $\delta_{\text{H}} 4.08$ with J value 6.8 Hz and a three-proton triplet signal resonated at $\delta_{\text{H}} 0.90$ with J value 6.8 Hz were assigned to $-\text{OCH}_2$ proton and $-\text{CH}_3$ proton respectively. A multiplet signal resonated at $\delta_{\text{H}} 1.82$ indicating the presence of $(-\text{C}_{16}\text{H}_{32}-)$ proton.

3.1.2. 2-(4-(4-octanyloxyphenylcarboxy)benzylidene)malononitrile (**2**).

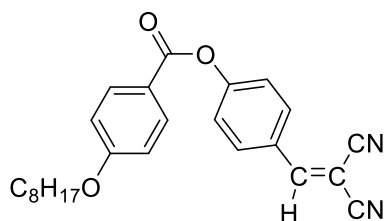


Figure 2 Chemical structure of 2-(4-(4-octanyloxyphenylcarboxy)benzylidene)malononitrile (**2**).

The compound 2-(4-(4-octanyloxyphenylcarboxy)benzylidene) malononitrile (**2**) in its IR spectrum showed absorption stretching band at 3011.98 cm^{-1} due to the presence of aromatic C-H bond. An absorption stretching band at 1591.34 cm^{-1} due the presence of aromatic C=C bond. The compound displayed characteristic absorption band for C=O of ester functionality at 1738.90 cm^{-1} . An absorption stretching band at 1699.98 cm^{-1} due to the presence of C=C (Olefinic) bond. An absorption stretching band at 2223.06 cm^{-1} due to the presence of -CN group. Two absorption stretching bands at 1166.02 cm^{-1} and 1056.07 cm^{-1} due to the presence of C-O (ether) group.

Again, the compound 2-(4-(4-octanyloxyphenylcarboxy)benzylidene)mlononitrile (**2**) in its $^1\text{H-NMR}$ spectrum displayed four two-proton doublet signals resonated at $\delta_{\text{H}} 8.16$, $\delta_{\text{H}} 8.03$, $\delta_{\text{H}} 7.46$ and $\delta_{\text{H}} 7.02$ with J values 8.1 Hz, 8.8 Hz, 8.8 Hz, and 8.8 Hz respectively were designated to eight aromatic protons of H-2', H-2'', H-3', H-3'', H-5', H-5'', H-6', H-6'' respectively. The peak in the downfield region resonated at δ_{H}

7.79 indicating the presence of C=CH proton. A two-proton triplet signal resonated at δ_H 4.07 with J value 6.4 Hz indicating the presence of $-\text{OCH}_2$ proton. The spectrum also displayed a three-proton singlet signal resonated at δ_H 0.92 with J value 6.4 Hz. A twelve-proton multiplet signal resonated at δ_H 1.85 indicating the presence of ($-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$) proton.

3.1.3. Ethyl 2-cyano-3-(4-hexadecanyloxyphenyl) acrylate (3).

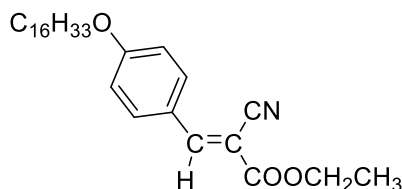


Figure 3 Chemical structure of ethyl 2-cyano-3-(4-hexadecanyloxyphenyl) acrylate (3).

The compound ethyl 2-cyano-3-(4-hexadecanyloxyphenyl)acrylate (3) in its IR spectrum exhibited characteristic band absorption for C=O ester functionality at 1719.61 cm^{-1} . The absorption band at 2218.23 cm^{-1} was due to $-\text{CN}$ stretch while bands at 1716.72 cm^{-1} and 1586.52 cm^{-1} were assigned to the existing of C=C (olfinic) and aromatic C=C bond respectively. $=\text{C}-\text{H}$ stretching appeared at 3079.49 cm^{-1} . Two absorption stretching bands at 1179.52 cm^{-1} and 1095.61 cm^{-1} were indicating the presence of C-O (ether) group.

Again, the compound ethyl 2-cyano-3-(4-hexadecanyloxyphenyl)acrylate (3) in its ^1H -NMR spectrum showed a one-proton singlet signal resonated at δ_H 8.1 indicating the presence of $\text{CH}=\text{C}$ proton. The ^1H -NMR spectrum exhibited two two-proton doublet signals resonated at δ_H 8.02 and δ_H 7.0 with J value 8.8 Hz were designated to H-2, H-6 and H-3, H-5 protons respectively. The spectrum also displayed a two-proton quartet signal resonated at δ_H 4.38 with J value 7.2 Hz which is indicative for the presence of $-\text{CH}_2-$ of the (ethyl ester) proton while a triplet signal resonated at δ_H 0.90 with J value 6.4 Hz designated the presence of $-\text{CH}_3$ proton. The ^1H -NMR showed a multiplet signal resonated at δ_H 1.43 indicating the presence of ($-\text{C}_{14}\text{H}_{28}-$) group. The ^1H -NMR also exhibited a two-proton triplet signal resonated at δ_H 4.06 with J value 6.4 Hz indicating the presence of $-\text{OCH}_2-$ group.

3.2. Pharmacokinetic investigation

Chemical's "absorption, distribution, metabolism, excretion, and toxicity (ADMET)" are all important facets of pharmacological analysis. The *AdmetSAR* (<https://lmmd.ecust.edu.cn/admetSar1/predict/?smiles=CC1%3DCC%3DCC%3DC1&action=A>) online tool was used to predict the ADMET properties of all chemicals

[19]. The “prediction of activity spectra for substances (PASS)” (<https://way2drug.com/PassOnline/index.php>) web tool was further employed to predict drug-like organic molecules with biological activity profiles based on the chemical's structural formula. In each case, the results were generated using SMILES (simplified molecular input line entry system) and structural data files [20].

3.2.1. ADMET analysis

In pharmacokinetics, the expression *ADMET* refers to the body's response to a drug. All of the features of possible medicine are studied by ADMET forecasting [21,22]. *AdmetSAR* results (**Table 2**) demonstrated that due to all α , β -unsaturated compounds e.g., dinitriles (**1-2**) and cyanoester (**3**) efficiently react with HIA (i.e., +0.997 to +1.000), nothing can be removed from the body more quickly through the urine and rectal systems [23]. Both dinitriles (**1-2**) resulted in an increased HIA results (+1.000). Again, all analogs displayed reduced human oral bioavailability (HOB) levels within the range of +0.250 to +0.430, suggesting that a human health risk may not occur from lower HOB [24]. A permeability component inside a single layer of the cancer cell line Caco-2, which is cultivated on permeable scaffolds, is frequently utilized to predict the diffusion of antibiotics and other oral medications [25,26]. All of the substances tested in our research offered substantial C2P results, implying that the body quickly absorbs these drugs. Here, the C2P penetration of analyzed compounds (**1-3**) varies from +0.685 to +0.744. The severely restricted "blood-brain barrier (BBB)" regulates the passage of compounds, electrically charged particles, as well as cells among the cerebral cortex and other parts of the body. It was rather surprising that all of the analogs tested in this study exhibited a positive impact on BBB, ranging from +0.638 to +0.824. The favorable BBB response indicates that they are not passing it quickly, which is concerning [24]. Here, all of the studied analogs exhibited quite less BBB activity, which is positive. Again, the tested dinitriles (**1-2**) demonstrated *p*-glycoprotein inhibitions (*p*-GpI) (e.g., 0.507 and 0.702, respectively), but cyanoester (**3**) showed just negative *p*-GpI suppression (e.g., 0.895). In this investigation, all compounds exhibited low non-substrate inhibitory effects on the main cytochrome P450 enzyme CYP2C9, resulting in favorable results (e.g., 0.797 to 0.865). A positive suppression of C2P has an impact on several harmful medicines that affect the enzyme [27,28]. Innovative drugs (2-3) weakly block (e.g., 0.756 and 0.986) the human "ether- α -go-go-related gene (hERG)," however compound **1** suppresses the hERG, suggesting lower than conventional therapies, causing a risk of long QT disorders as well as major cardiac side effects such as sudden death [29]. In our analysis, none of the materials demonstrated evidence of carcinogenic activities. All analogs displayed acute oral toxicology (AOT) grade III, indicating mildly risky except compound (**2**) which showed AOT level IV, and the

projected LD₅₀ ranged from 1.822 to 1.,939 mol/kg, indicating it's fairly significant [30].

3.2.2. PASS studies

In our investigation, Table 3 shows the Pa values (chance of a molecule becoming active) for tested α , β -unsaturated chemicals [1-3] with different biological activity. Analogs showed significant biological activity, such as antipyretic (0.220 - 0.377), anti-inflammatory properties (0.301 - 0.602), gastrin inhibitory (0.144 - 0.582), antidiabetic symptomatic (0.134 - 0.289), antineoplastic (0.190 - 0.342), antiparasitic (0.245 - 0.271), and antiviral (0.250 - 0.519) effects. Dinitrile (1) had most potent anti-inflammatory and antiviral potential, with values of 0.602 and 0.519, respectively, whereas compounds 2-3 had considerable gastrin inhibitory effects of 0.567 and 0.582. This study found that all α , β -unsaturated drugs had less adverse effects, yet offering less effective anti-inflammatory, antipyretic, and antiviral properties. Analogs could explain the minor adverse implications of α , β -unsaturated dinitriles as well as esters on the animal body.

Table 2 ADMET properties of synthesized compounds (1-3).

Serial no.	Absorption			Distribution		Metabolism	Toxicity			
	HIA	HOB	C2P	BBB	p-GpI	CYP450/2C9	hERG	Carcinogen	AOT	RAT
1	+1.000	+0.290	+0.685	+0.824	0.507 (I)	0.829 (NS)	0.573 (I)	0.788 (NC)	III	1.939
2	+1.000	+0.430	+0.688	+0.638	0.702 (I)	0.797 (NS)	0.756 (WI)	0.846 (NC)	IV	1.837
3	+0.997	+0.250	+0.744	+0.646	0.895(NI)	0.865 (NS)	0.986 (WI)	0.521 (NC)	III	1.822

Table 3 PASS predicted biological activities of tested compounds (1-3).

Serial no.	Antipyretic	Anti-inflammatory	Gastrin inhibitor	Antidiabetic symptomatic	Antineoplastic	Antiparasitic	Antiviral	
							Activity	Virus
1	0.220	0.602	0.144	0.134	0.245	0.271	0.519	Rhino
2	0.377	0.301	0.567	0.289	0.342	0.271	0.250	Herpes
3	0.256	0.480	0.582	0.278	0.190	0.245	0.259	Adeno

4. Conclusion

In this study, we demonstrated the production of α , β -unsaturated dinitriles as well as cyanoester by microwave radiation using ammonium acetate under solvent free conditions. This method offers multiple advantages, including high yields, relatively fast times for reaction, low cost, quick experimental and extraction procedures, and compatibility with green chemistry protocols. Again, the study observed that synthesized α , β -unsaturated compounds had fewer side effects in biological activity.

Thus, the study's activity data will guide future drug design and also the synthesis of various α , β -unsaturated cyanoesters and dinitriles analogues.

Declaration of competing interest

The authors declare that any known competing financial interests or personal relationships could have influenced none of the work reported in this study.

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