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GC–MS and FTIR evaluation of the six benzoyl-substituted-1-pentylindoles: Isomeric synthetic cannabinoids

Forrest T. Smith [a], Jack DeRuiter [a], Karim Abdel-Hay [a,b], C. Randall Clark [a,*]

[a] Department of Drug Discovery and Development, Harrison School of Pharmacy, Auburn University, Auburn, AL 36849, United States
[b] Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Alexandria University, Alexandria 21521, Egypt

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ABSTRACT

This report compares the GC–MS and FTIR properties of all 6 regioisomeric benzoyl substituted-1-*n*-pentylindoles. These compounds have the benzoyl-group attached at each of the possible ring substituent positions of the indole ring. The six compounds have the same elemental composition $C_{20}H_{21}NO$ yielding identical nominal and exact masses. Additionally, the substituents attached to the indole ring, benzoyl- and 1-*n*-pentyl-groups, are identical for all six isomers. The electron ionization mass spectra show equivalent regioisomeric major fragments resulting from cleavage of the groups attached to the central indole nucleus. Fragment ions occur at *m*/*z* 77 and 105 for the phenyl and benzoyl cations common to all six regioisomeric substances. Fragmentation of the benzoyl and/or pentyl groups yields the cations at *m*/*z* 234, 220, 214, 186 and 144. While the relative abundance of the ions varies among the six regioisomeric substances the 1-*n*-pentyl-3-benzoylindole and 1-*n*-pentyl-5-benzoylindole share very similar relative abundances for the major fragment ions.

Chromatographic separations on a capillary column containing a 0.5 μm film of 100% trifluoropropyl methyl polysiloxane (Rtx-200) provided excellent resolution of these six compounds. The elution order appears related to the relative distance between the two indole substituted groups. The latest eluting compounds (highest retention time) have the two substituents on opposite sides of the indole nucleus. Infrared absorption spectral data show the carbonyl absorption band for each of the benzoylindoles and provide distinguishing and characteristic information to individualize each of the regioisomers in this set of compounds.

1. Introduction

A number of new designer substances have appeared in forensic drug samples during the past decade. The synthetic cannabinoid series of designer drugs include direct analogues of delta-9-tetrahydrocannabinol (THC) and 5-(dimethylalkyl)-2-[3-hydroxycyclohexyl]-phenol (CP-47,497) as well as the 1-alkyl-3-acylindoles (JWH compounds) [1,2]. These compounds were initially used to investigate the cannabinoid receptors and their pharmacology. The "JWH" compounds act as full agonists at both the CB_1 and CB_2 cannabinoid receptors, with some selectivity for CB_2 [3]. CB_1 is found predominantly in the brain and is responsible for most of the overt pharmacological effects of the cannabinoids while the CB_2 receptor is primarily present in peripheral tissues. In spite of any CB_2 selectivity, many of the synthetic cannabinoids are more potent as agonists than THC at CB_1 receptors. Some 1-alkyl-3-acylindoles have affinity for the cannabinoid brain (CB_1) receptor five times greater than that of THC and have been shown to produces psychoactive effects in animals similar to those of THC [4].

The reported structure-activity relationships have led in recent years to the emergence of a variety of 1-alkyl-3-acylindoles and other synthetic cannabinoids in the clandestine drug market. These compounds were originally referred to as "Spice" or "K2" and marketed as legal natural products described as "herbal incense" or "herbal smoking blends" [5,6]. Subsequent analysis revealed, however, that these products were in fact synthetic compounds. Many synthetic cannabinoids with psychotropic effects have been identified in clandestine drug samples in recent years [7,8]. Thus the emergence of these synthetic cannabinoids represents a recent phenomenon in the designer drug market, focusing primarily on those indole derivatives with structures known to produce the desired CNS effects.

A number of structure-activity studies have been published with respect to the activity of 3-acyl-1-alkylindole derivatives at the CB_1 receptor, the receptor that mediates the cannabis-like psychologic effects of these drugs [4,9,10,11]. These studies have focused primarily on modification of the substituents on positions 1, 2 and 3 on the indole nucleus. Varying the substituent at the 3-position of the indole

* Corresponding author. Tel.: +1 334 844 8326; fax: +1 334 844 8331.
E-mail address: clarkcr@auburn.edu (C. Randall Clark).

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ring has been most extensively investigated in this series of compounds. The 1,3-substitution pattern on the indole ring has been studied extensively for cannabinoid receptor affinity and pharmacological activity as well as analytical evaluation using modern techniques such as nuclear magnetic resonance (NMR) and gas chromatographic mass spectrometric (GC–MS) analysis [12,13,14].

The regioisomer issue in forensic drug analysis is extremely important when some molecules are legally controlled drugs or controlled precursor substances. Such regioisomeric compounds often possess mass spectral equivalency and similar chromatographic elution properties. Those substances co-eluting in the chromatographic system and having common mass spectra could be misidentified. Furthermore, the ability to distinguish between these regioisomers directly enhances the specificity of the analysis for the target molecules. This issue is made even more critical when numerous regioisomeric precursor substances are commercially available in those drug categories produced by totally synthetic methods.

This paper directly compares a series of all six regioisomeric 1-*n*-pentylbenzoylindoles having the benzoyl-group at each of the possible ring substituent positions of the indole ring. The structures for the model compounds in this study are shown in Fig. 1. The 1,3-substitution pattern as shown for Compound 2 in Fig. 1 is the classic pattern for the indole derivatives often described as synthetic cannabinoids. While the 1,3-substitution pattern is directly available from indole as a synthetic starting point all five of the other possible regioisomeric 1-*n*-pentyl-benzoylindoles are available from other commercially available synthetic precursor materials.

2. Experimental

2.1. Instrumentation

GC–MS System 1 consisted of an Agilent Technologies (Santa Clara, CA) 7890A gas chromatograph and an Agilent 7683B auto injector coupled with a 240 Agilent Ion Trap mass spectrometer. The mass spectral scan rate was 2.86 scans/s. The GC was operated in splitless mode with a helium (grade 5) flow rate of 0.7 mL/min and the column head pressure was 10 psi. The MS was operated in the electron impact (EI) mode using an ionization voltage of 70 eV and a source temperature of 230 °C. The GC injector was maintained at 250 °C and the transfer line at 280 °C. The GC studies were performed on a column (30 m × 0.25 mm i.d.) coated with 0.5 µm 100% trifluoropropyl methyl polysiloxane (Rtx-200) purchased from Restek Corporation (Bellefonte, PA). The separations were obtained using a temperature program consisting of an initial hold at 80 °C for 1.0 min, ramped up to 300 °C at a rate of 30 °C/min, held at 300 °C for 0.5 min then ramped to 340 °C at a rate of 5 °C/min and held at

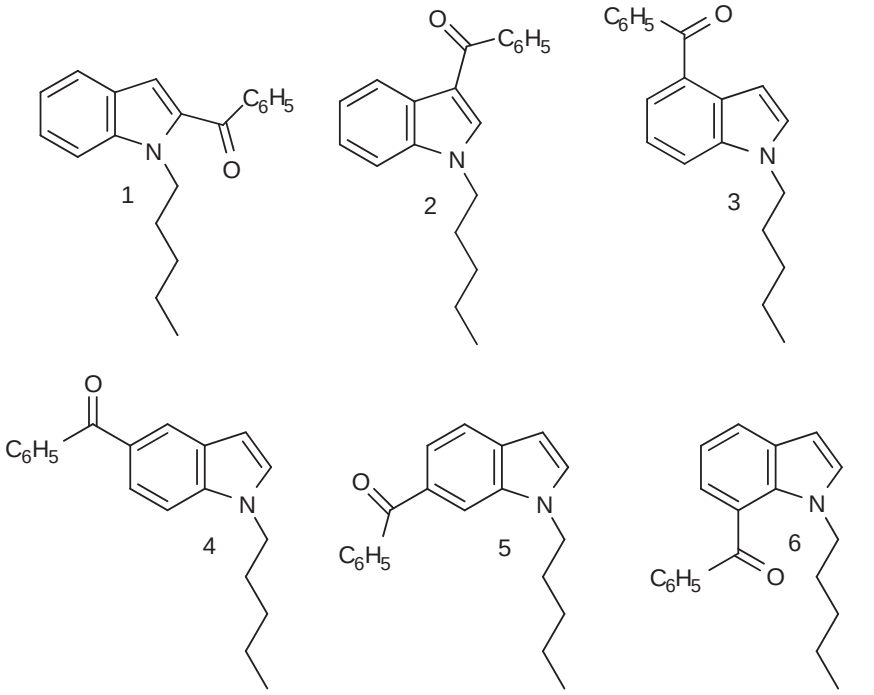

Fig. 1. Structures of the regioisomeric 2-, 3-, 4-, 5-, 6-, and 7-benzoyl-1-*n*-pentylindoles in this study.

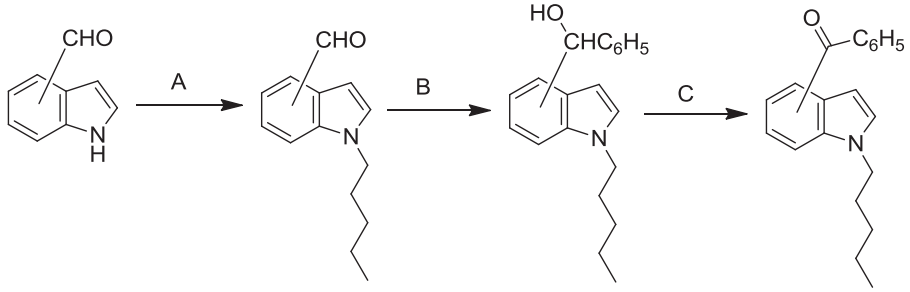

Fig. 2. General synthetic scheme for the compounds in this study. *A*=sodium hydroxide and 1-bromo-*n*-pentane; *B*=phenylmagnesium bromide; *C*=pyridinium dichromate.

340 °C for 25.0 min. Samples were dissolved and diluted in high-performance liquid chromatography-grade acetonitrile (Fisher Scientific, Fairlawn, NJ) and introduced via the auto injector using an injection volume of 1 μL.

GC–MS System 2 consisted of an Agilent Technologies (Santa Clara, CA) 7890A gas chromatograph and an Agilent 7683B auto injector coupled with a 5975C VL Agilent mass selective detector. In this system the GC injector was maintained at 300 °C and the transfer line at 325 °C, all other experimental parameters were the same as GC–MS System 1.

Attenuated total reflection infrared (ATR FTIR) spectra were obtained on a Shimadzu IRAffinity-1 Fourier transform infrared

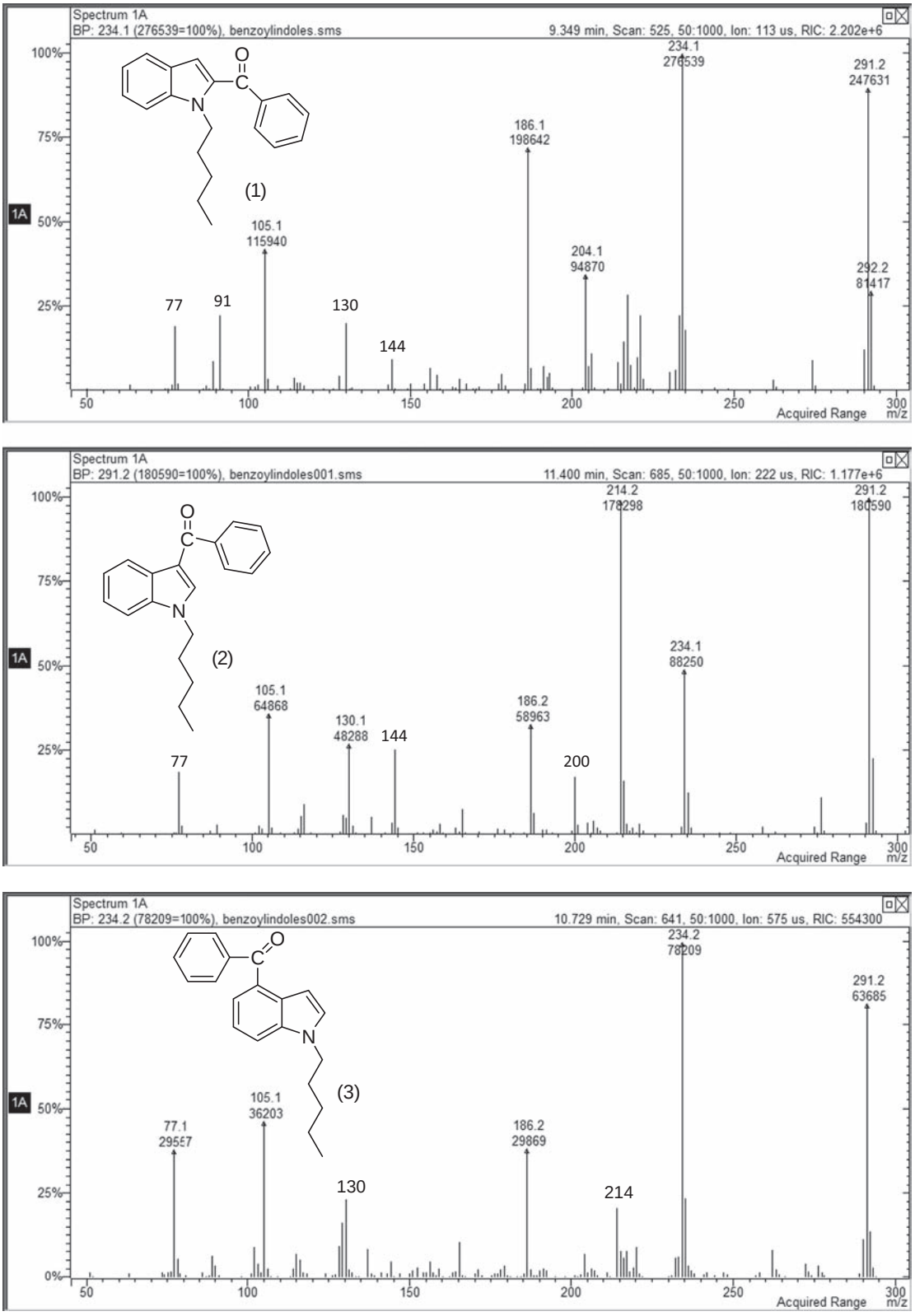

Fig. 3. Mass spectra for the individual benzoyl-1-*n*-pentylindole isomers. GC–MS system 1.

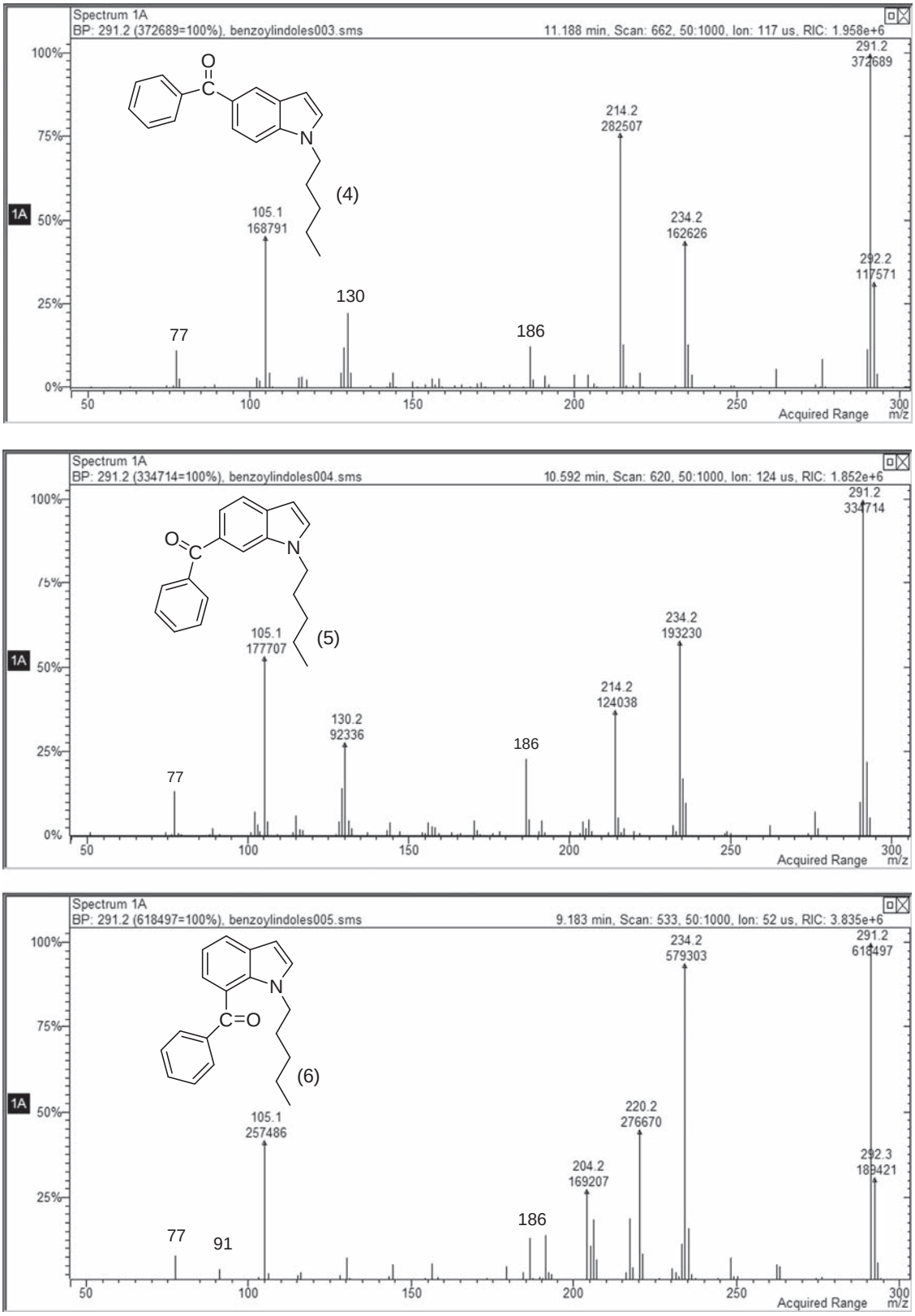

Fig. 3. (*continued*)

spectrophotometer (Kyoto, Japan) equipped with a DLATGS detector with temperature control system at a resolution of 4 cm^{-1} with an aperture of 3.5 mm and scan rate of 10 scans per second. The FTIR spectrophotometer was equipped with MIRacle Single Reflection Horizontal ATR Accessory (Pike Technologies, WI). The single-reflection sampling plate of the accessory has a 1.8 mm round crystal surface allowing reliable analysis of small samples. FTIR spectra were recorded in the range of 4000–520 cm^{-1}.

The samples were prepared by dissolving the solid or oily compounds in acetonitrile and introducing the resulting solutions in small volumes to the center of the single-reflection sampling plate.

2.2. Synthetic methods

2.2.1. 1-n-Pentylindole

A mixture of sodium hydride in mineral oil and a solution of indole in DMF were stirred under dry nitrogen for 30 min. 1-Pentylbromide was added to the indole/NaH mixture and heated for 1 h then cooled and the mixture poured into water and extracted with methylene chloride. The combined methylene chloride extracts were washed with water, dried and evaporated to yield the desired 1-*n*-pentylindole product.

2.2.2. 1-n-Pentyl-3-benzoylindole

A solution of 1-*n*-pentylindole was dissolved in methylene chloride under nitrogen and added to a three-neck flask. The reaction mixture was cooled and 1.0 M dimethylaluminum chloride in hexane was added via a syringe/septum. Benzoyl chloride in dry methylene chloride was added over a period of 5 min to the reaction mixture and then stirred over an ice bath under nitrogen. The reaction mixture was quenched by careful addition of cold 1 N HCl and the HCl solution was extracted with methylene chloride. The combined methylene chloride extracts are washed with water then saturated sodium bicarbonate and dried over potassium sulfate to yield the product, 1-*n*-pentyl-3-benzoylindole.

2.2.3. 1-n-Pentylindole aldehydes

A mixture of pulverized sodium hydroxide and a solution of the appropriate indole aldehyde in DMF were stirred with 1-pentylbromide at room temperature. The mixture was poured into water and extracted with ethylacetate and the combined extracts were washed with water, dried and evaporated to yield the desired 1-*n*-pentylindole aldehyde product.

2.2.4. 2-, 4-, 5-, 6-, and 7-benzoyl-1-n-pentylindoles

A solution of the appropriate 1-pentylindole aldehyde was dissolved in distilled diethylether and added to a dry flask containing a nitrogen atmosphere. A solution of phenylmagnesium bromide in diethyl ether was added using a syringe and the resulting solution stirred at room temperature. The excess reagent was consumed by addition of saturated ammonium chloride and extracted with diethylether. The ether solution was dried over sodium sulfate and evaporated to dryness under reduced pressure to yield an oily viscous residue.

The oily material was dissolved in dimethylformamide (DMF) and added to a solution of pyridinium dichromate in DMF. The resulting mixture was stirred at room temperature then mixed with diethylether. The organic layer was then washed with water, dried with sodium sulfate, evaporated and purified by spinning band chromatography to give the desired product.

3. Results and discussion

3.1. Synthetic methods

Differentiation of isomers can be a critical issue in forensic drug chemistry when one isomer is a controlled substance. A large number [1,2,4,9–11] of 1-alkyl-3-acylindoles are known to have significant affinity at cannabinoid receptors. The isomeric substituted

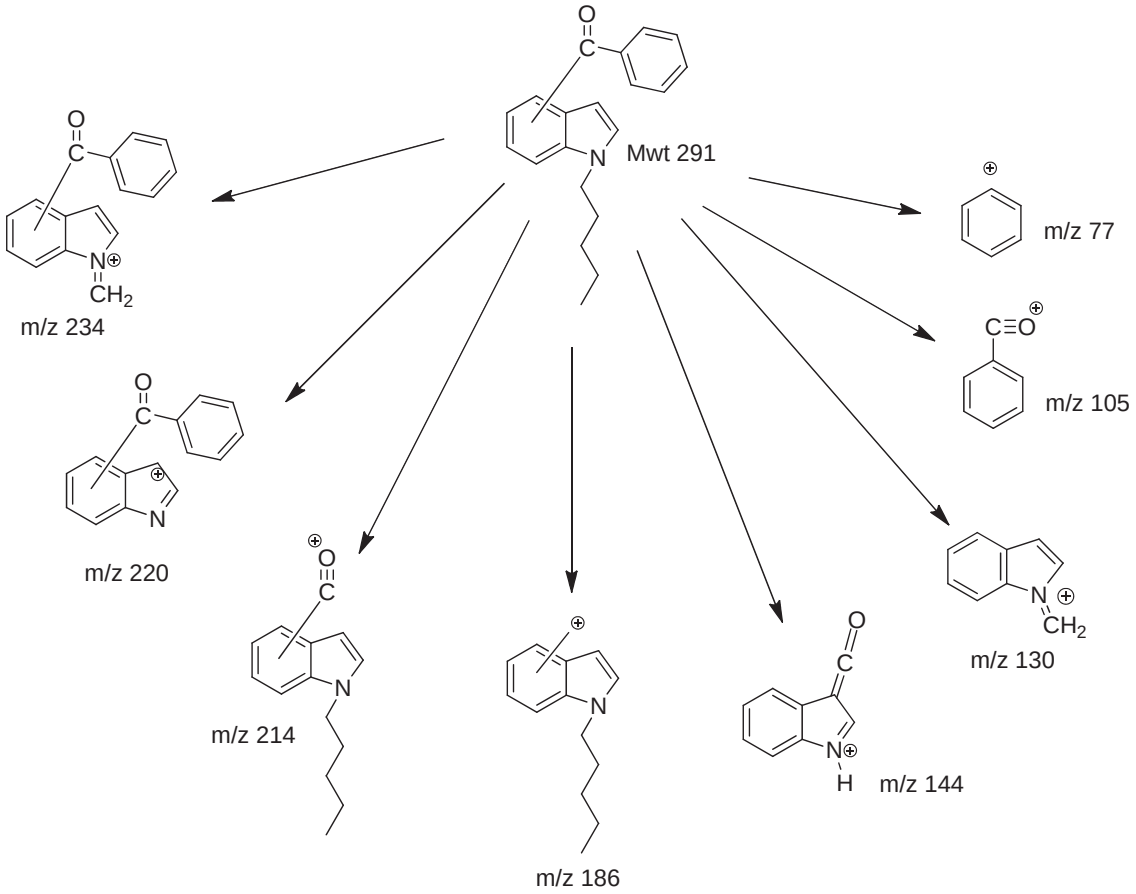

Fig. 4. Proposed structures for the major mass spectral fragments in the benzoyl-1-*n*-pentylindole.

alkylacylindoles are likely to share a number of equivalent analytical properties yet have different affinity at the cannabinoid receptors and variable biological activity.

The synthetic pathway for the regioisomeric 1-*n*-pentylindole aldehydes is illustrated in Fig. 2. The initial step in the synthetic sequence is the addition of the alkyl group (*n*-pentyl) to the indole aldehyde ring at the 1-position. The precursor indole aldehyde was directly alkylated at the 1-position nitrogen by treatment with sodium hydroxide and 1-bromo-*n*-pentane. The resulting individual regioisomeric *n*-pentylindole aldehydes were allowed to react with phenylmagnesium bromide to yield the corresponding substituted benzyl alcohol which upon oxidation gave the desired regioisomeric 1-*n*-pentylbenzoylindoles according to the synthetic pathway in Fig. 2. Five of the six isomers shown in Fig. 1 were prepared by the sequence described in Fig. 2. The 1-*n*-pentyl-3-benzoylindole was prepared directly from indole as a precursor substance as described previously [15].

3.2. Mass spectra

The mass spectra for the regioisomeric benzoyl-1-*n*-pentylindoles are shown in Fig. 3. These EI mass spectra were determined

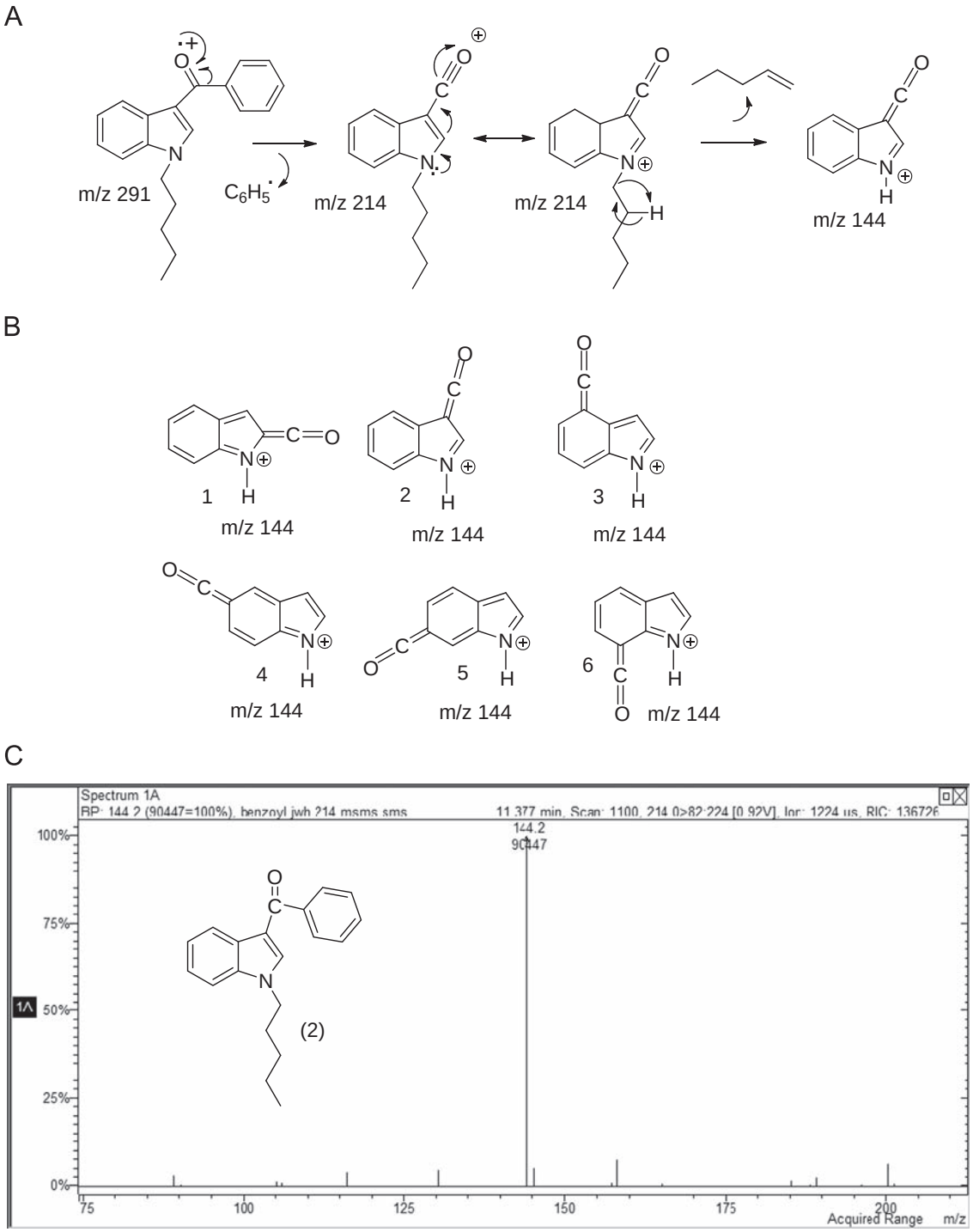

Fig. 5. (A) Example mechanism for the formation of the *m*/*z* 144 ion in 1-*n*-pentyl-3-benzoylindole. (B) Regioisomeric structures for the individual forms of the *m*/*z* 144 cation in the benzoyl-1-*n*-pentylindoles. (C) MS/MS spectrum of the *m*/*z* 214 fragment for 3-benzoyl-1-*n*-pentylindole. GC–MS system 1 (operated in MS/MS mode).

individually following sample injection using GC–MS System 1. All six compounds show a significant molecular ion peak at *m/z* 291of high relative abundance. The molecular ion at *m/z* 291 or the *m/z* 234 ion occurs as the base peak for each of the six compounds. The *m/z* 234 ion is the immonium cation resulting from the loss of 57 Da from the molecular ion. Additionally, compound 2 shows a major fragment at *m/z* 214 $(M\text{-}77)^+$ of similar relative abundance to the base peak molecular ion.

The structures for the major fragment ions in the spectrum for these regioisomeric benzoyl-1-*n*-pentylindoles are shown in Fig. 4. These ions primarily form as a result of fragmentation of the substituents attached to the indole ring with a major fragment occurring at *m/z* 214. This fragment ion represents the loss of mass 77 from the molecular ion at *m/z* 291 and a likely source of this *m/z* 214 peak is the loss of the phenyl group from the molecular ion as shown in the fragmentation scheme in Fig. 4. A comparison of the spectra for 1-*n*-pentyl-3-benzoylindole and the corresponding d_5-phenyl labeled 1-*n*-pentyl-3-benzoylindole [15] did not show a mass shift for the *m/z* 214 ion confirming the loss of the phenyl group as the source of this ion at *m/z* 214. The d_5-phenyl labeled compound did show a +5 Da mass shift for the ions at *m/z* 77 and 105 confirming the deuterium labels in the phenyl portion of the benzoyl group attached at the 3-position of indole. The analogous processes would account for these ions in the other regioisomeric benzoyl-1-*n*-pentylindoles. The ion at *m/z* 144 occurs via hydrogen rearrangement from the positively charged nitrogen resonance form of the *m/z* 214 cation. This process results in the loss of 1-pentene and is illustrated in Fig. 5A using the isomer substituted at the 3-position. The structures for all six regioisomeric forms for the *m/z* 144 ion are shown in Fig. 5B and these ions form by a mechanism analogous to that shown in Fig. 5A. The *m/z* 144 ion is more prominent for isomers 1 and 2, those isomers in which the benzoyl group is substituted on the five membered pyrrole ring portion of the indole structure. MS/MS experiments confirmed the *m/z* 214 ion as the source of the *m/z* 144 ion. Fig. 5C shows the *m/z* 144 ion as the major product in the MS/MS spectrum of the *m/z* 214 fragment. The MS/MS spectrum for the *m/z* 291 molecular ion (spectrum not shown) did not show any *m/z* 144 ion. Thus the source of the *m/z* 144 ion is only the *m/z* 214 fragment in these spectra.

The *m/z* 234 ion in Fig. 4 is the nitrogen initiated alpha-cleavage fragmentation process resulting in the loss of C_4H_9 from the molecular ion, an equivalent pathway to that described for the formation of the base peak in the monosubstituted 1-pentylindole precursor substance [15]. The *m/z* 186 ion represents the loss of the benzoyl-group (M-105) from the molecular ion and this ion did not undergo a mass shift in the spectrum of the d_5-phenyl labeled 1-*n*-pentyl-3-benzoylindole [15] confirming this ion as resulting from the loss of the benzoyl-group from the molecular ion.

The ions clustering in the *m/z* 130 range likely represent the methylene indole species resulting from loss of the benzoyl group as well as four of the five carbons of the pentyl side chain. The structure for the final rearrangement product methylene indole occuring at *m/z* 130 is shown in Fig. 4. A comparison of the spectra in Fig. 3 shows some other unique ions which could be considered isomer specific. For example the *m/z* 91 ion appears to occur only for the 1,2- and 1,7-substitution patterns (see Fig. 3, Compound 1 and Compound 6). This unique ion for these compounds could result from the close proximity of the two indole substituents, close enough for significant intramolecular interactions. The *m/z* 91 benzyl/tropillium cation species likely occurs via an interactive rearrangement involving the two substituent groups. A similar process in these closely substituted 1,2- and 1,7-isomers likely produces the *m/z* 204 ion observed primarily for these two compounds.

While the relative abundance of some ions varies among the six regioisomeric substances, the major fragments occur at common masses for most of these regioisomeric compounds. Indeed, the 1-*n*-pentyl-3-benzoylindole and 1-*n*-pentyl-5-benzoylindole (Compounds 2 and 4) share very similar relative abundances for the major fragment ions. Compound 2, the 1-alkyl-3-acylindole species represents the common substitution pattern observed in most of the indole-type compounds with high affinity at the cannabinoid receptors. Thus, the differentiation of the 1-alkyl-3-acyl substitution pattern from all the other possible synthetic regioisomers can be a significant issue in forensic drug chemistry. These mass spectral studies provide some ions for differentiation however complete individualization based on mass spectra alone without the availability of all regioisomeric reference standards would remain quite challenging.

3.3. GC studies

The GC separation of the target compounds is shown in Fig. 6. This chromatogram was obtained using a 30 m capillary column coated with a 0.5 μm film of 100% trifluoro-propyl methyl polysiloxane (Rtx-200). The temperature program produced a column oven temperature of over 300 °C in less than 9 min and a final high temperature of 340 °C. Under these conditions this relatively polar stationary phase provided excellent resolution of these six regioisomeric compounds. The first compound to elute in the chromatogram in Fig. 6 is the 1-*n*-pentyl-7-benzoylindole isomer followed

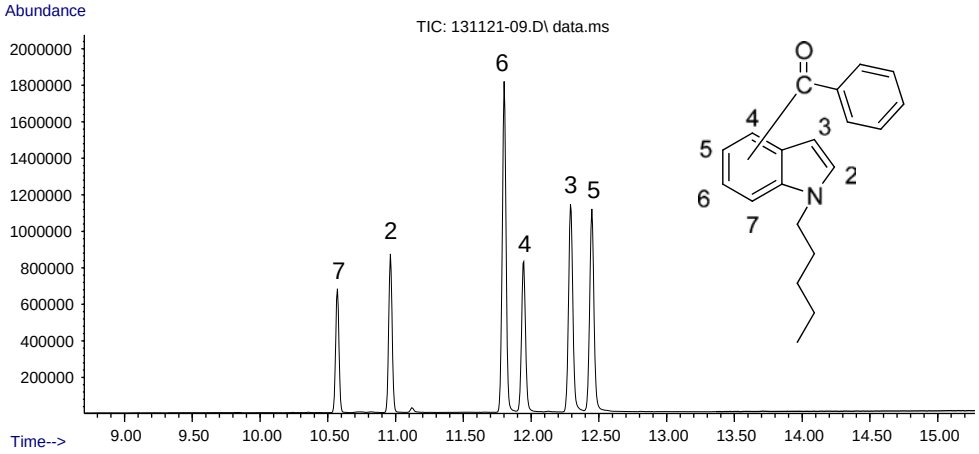

Fig. 6. GC separation of the regioisomeric 1-*n*-pentylbenzoylindoles in this study. GC–MS system 2. The numbers over the peaks correspond to the indole position of substitution for the benzoyl group.

by the 1-*n*-pentyl-2-benzoylindole isomer. These two isomers have in common the close intramolecular relationship between the two indole substituents. The *n*-pentyl and benzoyl groups are crowded on the same side of the indole ring in these two compounds suggesting that interactions between the two groups minimizes retention relative to the other isomers. Maximum

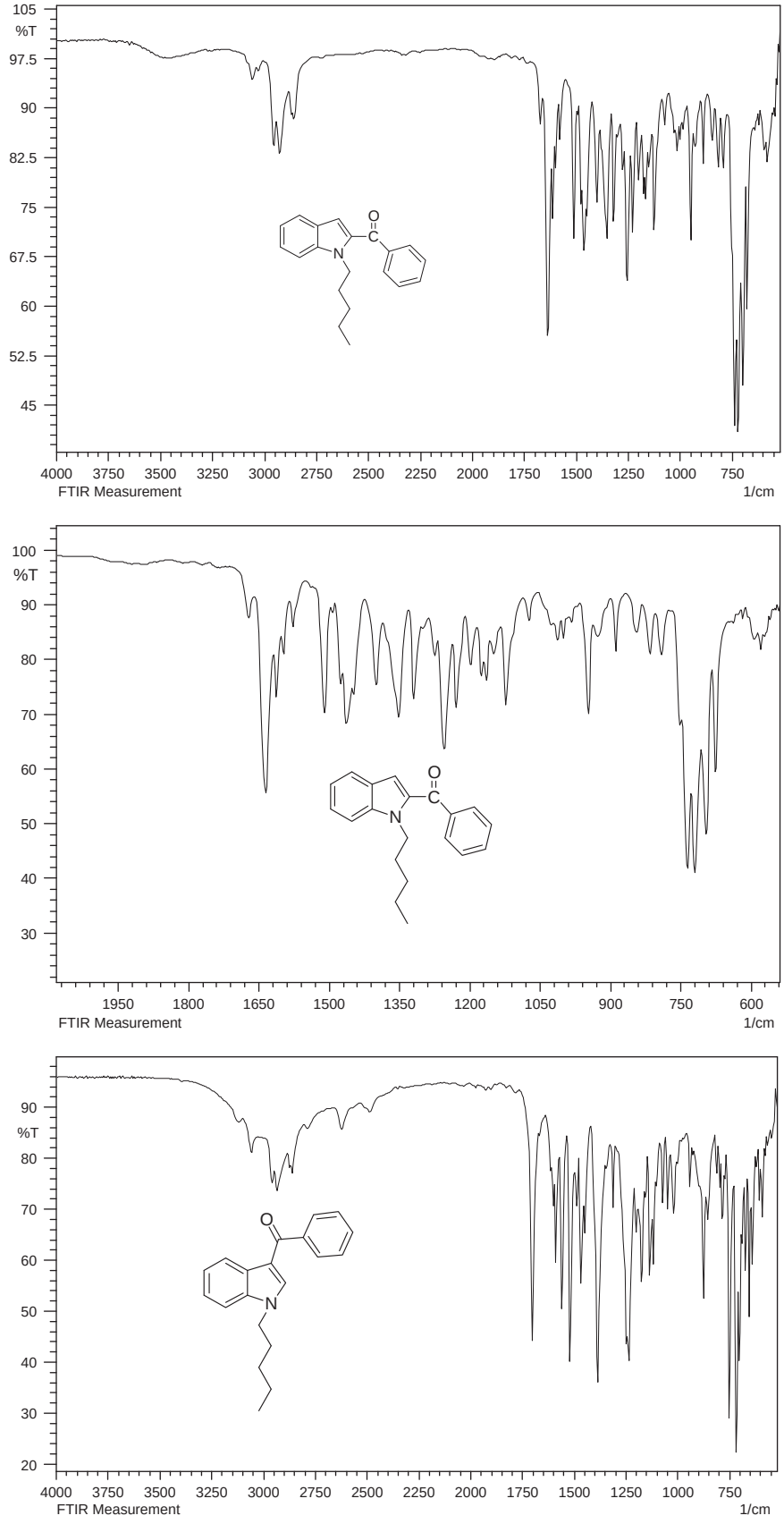

Fig. 7. FTIR spectra of the six regioisomeric 1-*n*-pentylbenzoylindoles in this study.

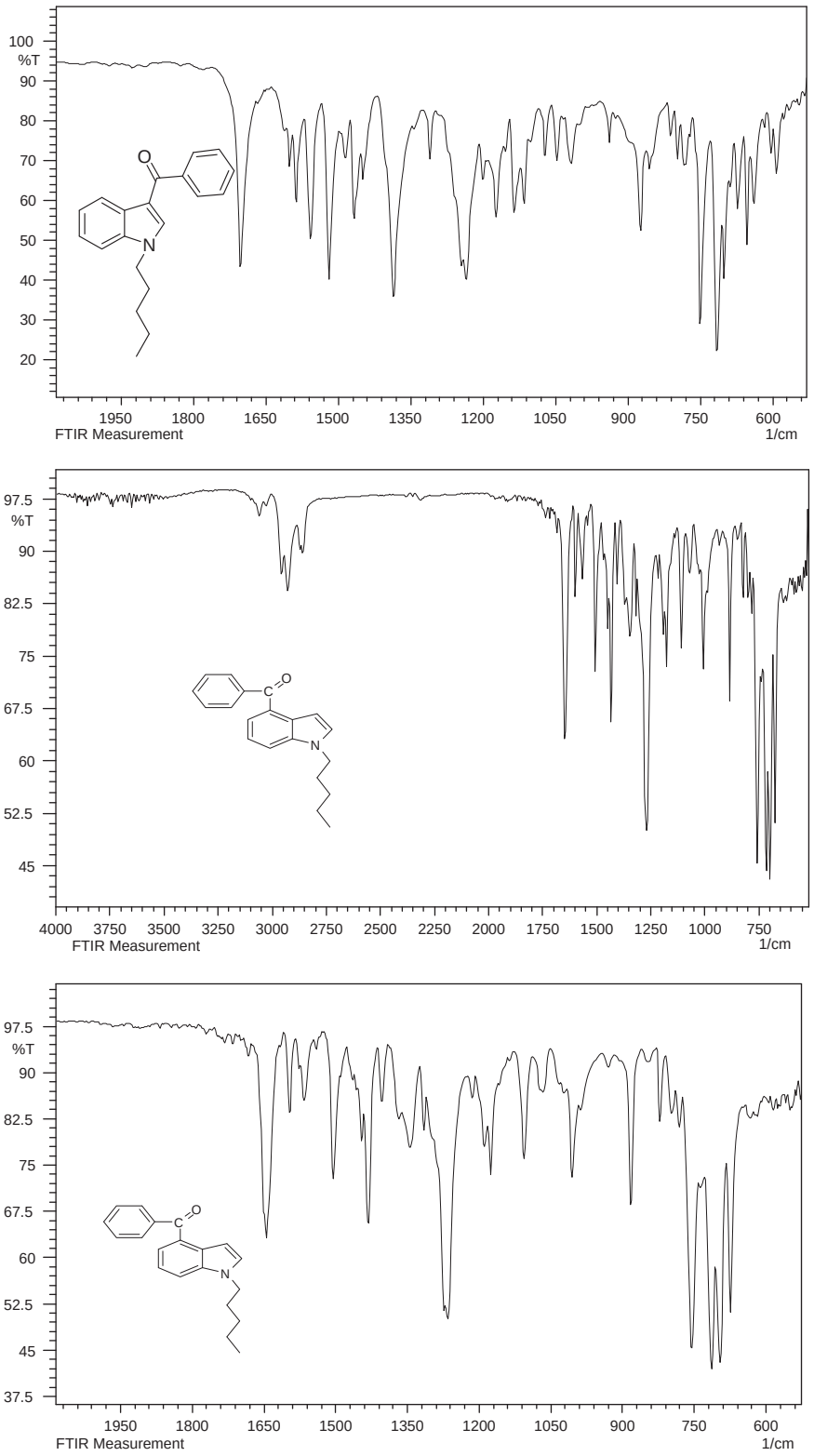

Fig. 7. (*continued*)

distance between the two substituent groups as observed in the 1,3- and 1,5-isomers appears to increase retention. The 1-*n*-pentyl-3-benzoylindole isomer and the 1-*n*-pentyl-5-benzoylindole isomer are the last to elute showing the highest retention times in this chromatographic system. Since the 1-alkyl-3-acylindoles are known to have significant affinity at cannabinoid receptors it can be an issue of significant forensic chemistry interest to distinguish the 1,3-isomers from the other possible regioisomeric substitution patterns. The 1,3- and 1,5-substitution patterns have similar chromatographic elution properties as seen in Fig. 6 and these two compounds showed a number of equivalent fragment ions of similar relative abundance in their mass spectra (see Fig. 3).

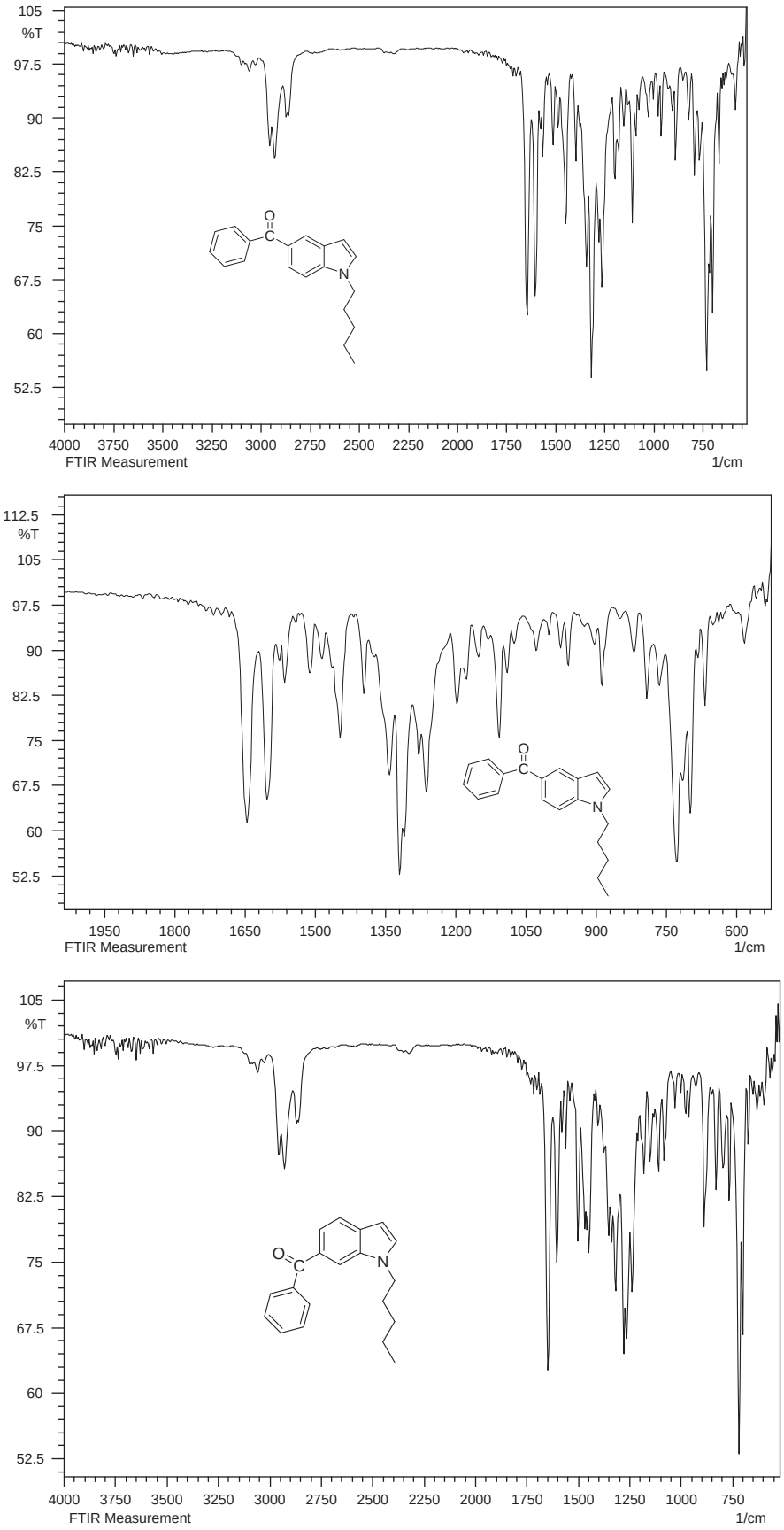

Fig. 7. (*continued*)

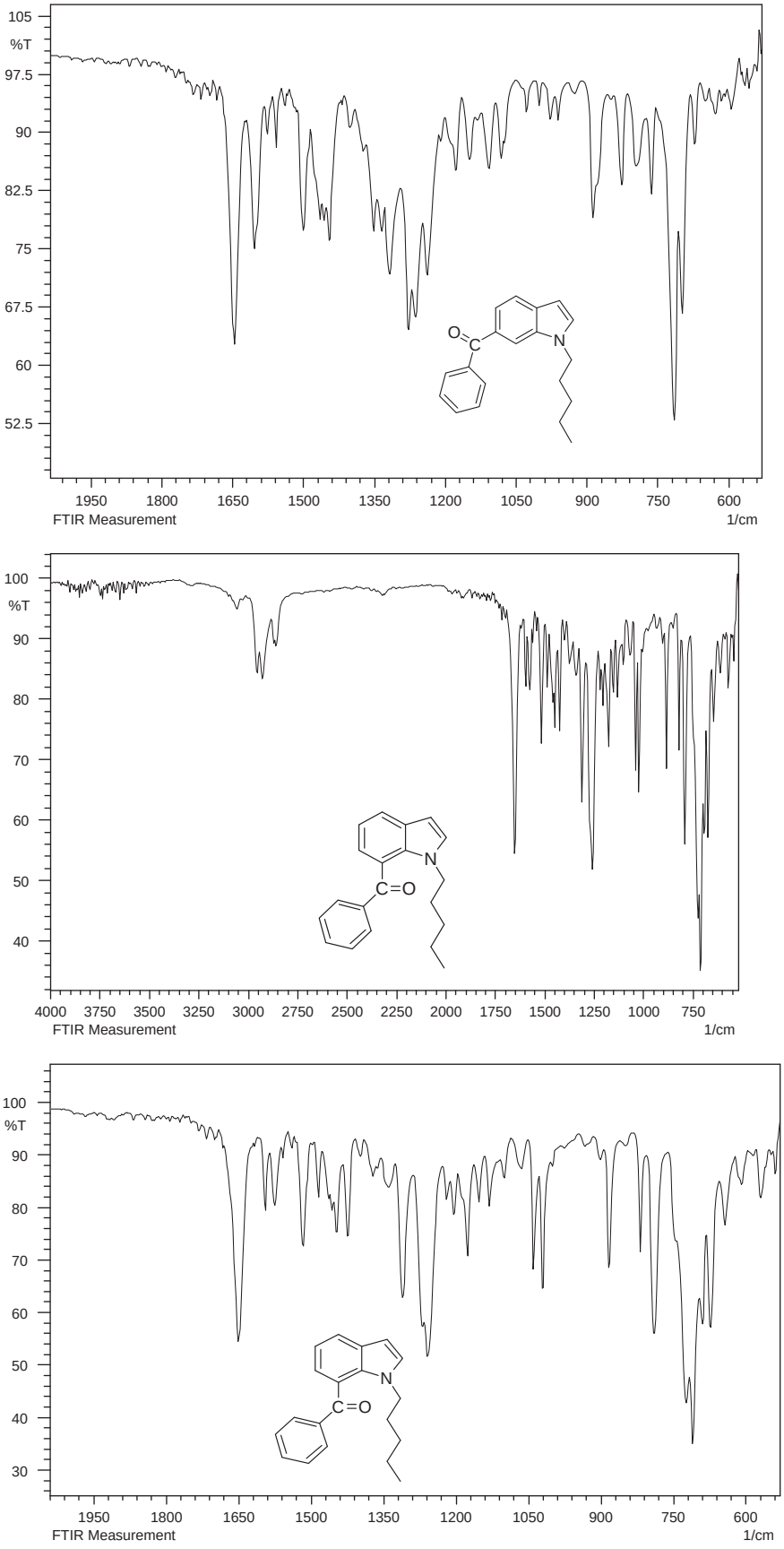

Fig. 7. (*continued*)

3.4. FTIR studies

Attenuated total reflection Fourier transform infrared spectroscopy (FTIR) was evaluated for differentiation among the regioisomeric compounds. This method has the possibility of yielding compound specificity without the need for chemical modification of the drug molecule. The spectra for the six compounds are shown in Fig. 7. The 1-*n*-pentyl-3-benzoylindole is characterized by the strong intensity carbonyl band at 1703 cm^{-1} which is shifted into a singlet of strong and equal intensity at 1635 cm^{-1} in the 1-*n*-pentyl-2-benzoylindole regioisomer and a singlet at 1645 cm^{-1} in the 1-*n*-pentyl-4-benzoylindole regioisomer. The FTIR spectrum of the 1-*n*-pentyl-5-benzoylindole shows strong doublet peaks at 1645 cm^{-1} and 1602 cm^{-1} which are shifted to a doublet at 1647 cm^{-1} and 1604 cm^{-1} for the 1-*n*-pentyl-6-benzoylindole regioisomers and a singlet at 1651 cm^{-1} in the 1-pentyl-7-benzoyl isomer.

The 1-*n*-pentyl-7-benzoylindole regioisomer has a relatively strong singlet at 1259 cm^{-1} which is shifted to a strong intensity doublet at 1276 cm^{-1} and 1263 cm^{-1} in the 1-*n*-pentyl-6-benzoyl isomer and a doublet at 1309 cm^{-1} and 1263 cm^{-1} in the 1-*n*-pentyl-5-benzoyl isomer. Also the FTIR spectrum of the 1-*n*-pentyl-2-benzoylindole shows weak doublet peaks at 1319 and 1255 cm^{-1} which are shifted to a strong singlet at 1234 cm^{-1} for the 1-*n*-pentyl-3-benzoyl regioisomers and a medium singlet at 1267 cm^{-1} for the 1-*n*-pentyl-4-benzoyl regioisomer. Finally the IR spectrum of the 1-*n*-pentyl-3-benzoyl regioisomer is characterized by a strong singlet at 1386 cm^{-1} which is absent in the IR spectra of all of the other five regioisomers involved in this study.

A direct comparison of the spectra for the 1,3-isomer and the 1,5-isomer shows significant differences in the carbonyl absorption bands for differentiation between these two regioisomers. These two isomers showed quite similar major mass spectral fragments as well as similar GC elution properties. Additionally, the 1-alkyl-3-acyl indoles represent the common substitution pattern observed in most of the indoles with synthetic cannabinoid significance. These results show that FTIR spectra provide useful data for differentiation among these regioisomeric compounds of mass spectral equivalence. Infrared absorption spectral data provide distinguishing and characteristic information to individualize the regioisomers in this set of compounds.

4. Conclusions

The electron ionization mass spectra show equivalent regioisomeric major fragments resulting from cleavage of the groups attached to the central indole nucleus. Fragment ions occur at *m*/*z* 77 and 105 for the phenyl and benzoyl cations common to all six regioisomeric substances. Fragmentation of the benzoyl and/or pentyl groups yield the cations at *m*/*z* 234, 220, 214, 186 and 144. While the relative abundance of the ions varies among the six regioisomeric substances the 1-*n*-pentyl-3-benzoylindole and 1-*n*-pentyl-5-benzoylindole share very similar relative abundances for the major fragment ions.

Chromatographic separations on a capillary column containing a 0.5 μm film of 100% trifluoropropyl methyl polysiloxane (Rtx-200) provided excellent resolution of these six compounds. The elution order appears related to the relative degree of distance between the two indole substituted groups. The latest eluting compounds (the 1,3- and 1,5-isomers) have the two substituents in a more linear relationship on the indole ring. Infrared absorption spectral data show the carbonyl absorption band for each of the benzoylindoles and provide distinguishing and characteristic information to individualize each of the regioisomers in this set of compounds. The carbonyl absorption for the 1-*n*-pentyl-3-benzoylindole occurs at 1703 cm^{-1} while that for the 1-*n*-pentyl-5-benzoylindole occurs as a doublet at 1645 cm^{-1} and 1602 cm^{-1}. These IR carbonyl absorption bands provide additional data for differentiation between these two compounds of similar MS and GC properties.

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