Mass Spectrometric Data of Commonly Abused Amphetamines and Their Derivatives — Cross Contributions of Ion Intensity between the Analytes and Their Isotopically Labeled Analogs

REFERENCE: Wang S-M, Chye S-M, Liu RH, Lewis RJ, Canfield DV, Roberts J: Mass spectrometric data of commonly abused amphetamines and their derivatives — Cross contributions of ion intensity between the analytes and their isotopically labeled analogs; *Forensic Sci Rev* 17:67; 2005.

ABSTRACT: With GC-MS as the preferred method and isotopically labeled analogs of the analytes as the internal standards (ISs) of choice for the analysis of drugs/metabolites in biological specimens, one important aspect associated with chemical derivatization (CD) is that the CD products derived from the analyte and the selected IS must generate ions suitable for designating the analyte and the IS; these ions cannot have significant cross-contribution (CC), i.e., contribution to the intensity of the ion designated for the analyte by the IS, and vice versa. With this in mind, the authors have reviewed literature and commercial information on common CD reagents and methods and conducted a thorough search of isotopically labeled analogs of commonly abused amphetamine-type drugs/metabolites that are commercially available. These ISs and analytes were then derivatized with various derivatization groups. These CD products were then analyzed by GC-MS and the resulting MS data are presented here in two forms: (a) systematic presentation of full-scan spectra; and (b) tabulation of CC data for ions with potential for designating the ISs and analytes. Many (if not most) of these full-scan spectra are not yet available in the literature and should be of daily reference value to forensic and clinical laboratories that are engaged in the analysis of these drugs/metabolites. Full-scan MS data were further used to select ion-pairs with potential for designating the analytes and ISs in quantitative analysis protocols. The CC data of these ion-pairs were evaluated using data collected under the SIM mode and summarized in table format. These data should save enormous amounts of time and efforts for practicing laboratories in their search for this analytical parameter.

KEY WORDS: Amphetamine, chemical derivatization, cross-contribution, ephedrine, GC-MS, internal standard, MBDB, MDA, MDEA, MDMA, methamphetamine, phenylpropanolamine.

INTRODUCTION

Chemical derivatization (CD) of analytes with active functional groups is now a universal and routine step in the process of preparing samples for gas chromatography-mass spectrometric (GC-MS) analysis. The objectives of CD can be grouped into the following three basic categories [42]:

- Increasing compatibility with the chromatographic environment;
- Achieving required separation or improving separation efficiency; and
- Improving detection and structure-elucidation efficiency.

Now that (a) GC-MS is the preferred method for the analysis of drugs/metabolites; (b) isotopically labeled analogs of the analytes are the internal standards (ISs) of choice; and (c) quantitative data of the analytes are generally needed in the analysis of drugs/metabolites in biological specimens; an additional aspect associated with CD has to be addressed. Specifically, CD products of the analyte and the selected IS must generate ions suitable for designating the analyte and the IS; these ions must not have significant cross-contribution (CC), i.e., contribution to the intensity of the ion designated for the analyte by the IS, and vice versa [5,41,44].

Scope

This study will be limited to the following amphetamine-type compounds: amphetamine (AM), methamphetamine (MA), (±)-phenylpropanolamine (PPA), 1S,2R(+)-ephedrine, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyethylamphetamine (MDEA), *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB). These drugs/metabolites were included for the following two reasons: (a) they are commonly abused and (b) isotopically labeled analogs of these drugs/metabolites are commercially available.

Common CD reagents and their general usage are shown in **Table 1**, while all CD reactions related to this study are further shown in chemical equation format (**Table 2**) using AM as the analyte for illustration. The authors have also searched for all isotopically labeled analogs of these drugs/metabolites that are commercially available. These ISs and analytes were then derivatized

Table 1. Silylation, acylation, and alkylation derivatizing reagents and characteristics

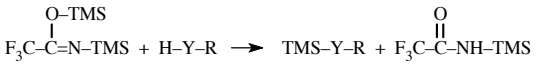
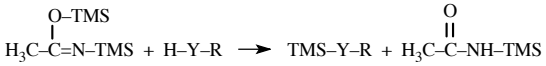
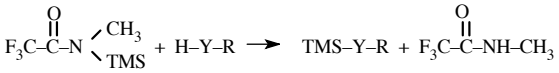
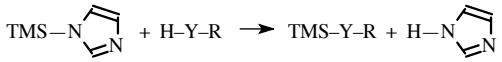
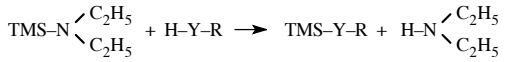
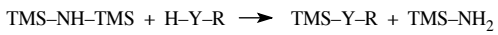
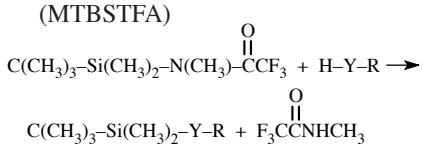
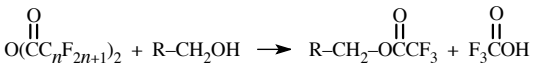
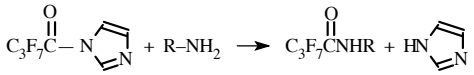
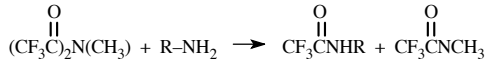
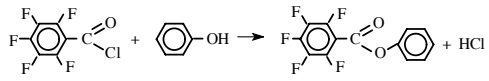
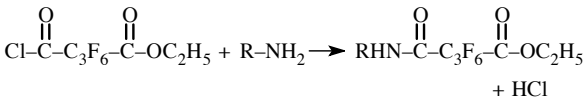
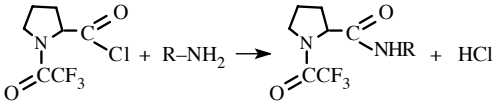
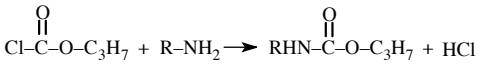
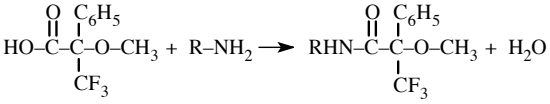
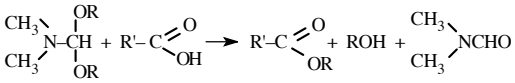
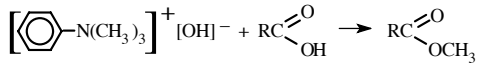
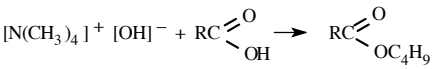
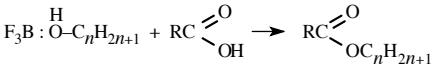
Reagent and reaction	Characteristics[a]
Silylation	
N,*O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) 	Reacts faster and more completely than BSA; Combine with 1% or 10% TMCS for hindered hydroxyl and other functionalities.
Trimethylchlorosilane (TMCS) 	Commonly used as a catalyst; Reaction by-product HCl.
N,*O*-Bis(trimethylsilyl)acetamide (BSA) 	Mild reaction conditions; Forms stable products; By-product TMS–acetamide may elute with analyte.
N-Methyltrimethylsilyltrifluoroacetamide (MSTFA) 	By-product TMS–acetamide very volatile; Most suitable for volatile trace analyte.
Trimethylsilylimidizole (TMSI) 	Reacts with hydroxyl but not amine; Suitable for hindered hydroxyl group.
Trimethylsilyldiethylamine (TMS-DEA) 	Basic reagent for amino and carboxylic acids.
Hexamethyldisilazane (HMDS) 	A weak TMS donor.
N-Methyl-*N*-(*t*-butyldimethylsilyl)trifluoroacetamide (MTBSTFA) 	Exceptionally strong yet mild reagent; Stable product in resisting hydrolysis; Combine with 1% *t*-butyldimethylchlorosilane catalyst for hindered alcohol and amine.
Acylation	
Anhydrides (TFAA, PFPA, HFBA, AA, TCAA)[b] 	Formation of fluoroacyl derivatives greatly increase volatility and improve detectivity in GC and MS, especially negative chemical ionization; Often used with bases, such as triethylamine.
Heptafluorobutyrylimidizole (HFBI) 	Reaction fast and mild, work best for phenol, alcohol and amine; By-product is not acidic.
N-Methyl-*N*-bis(trifluoroacetamide) (MBTFA) 	Reacts rapidly with primary and secondary amine, slowly with alcohol, phenol, and thiol; Mild reaction conditions with inert and volatile by-products.
Pentafluorobenzoyl chloride (PFBCI) 	Highly reactive, forming the most sensitive ECD derivatives of amine and phenol; Suitable for sterically hindered functionalities; Base often used to remove HCl produced.

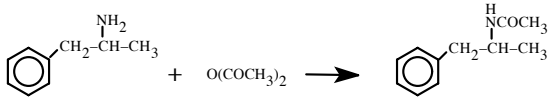
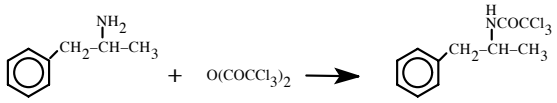
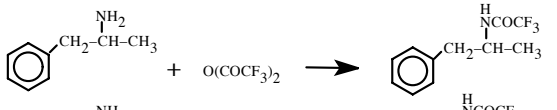
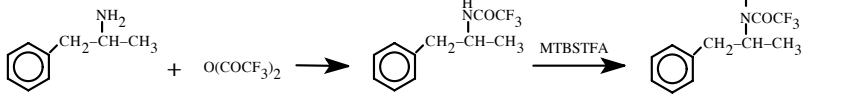
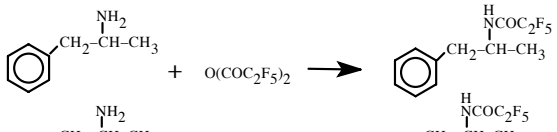
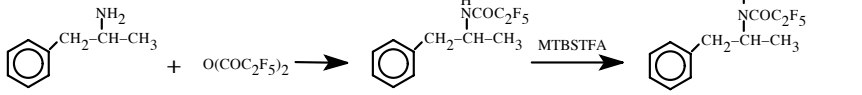
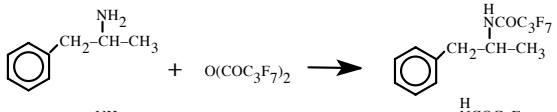
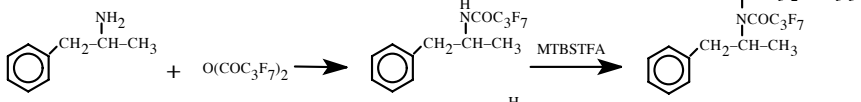
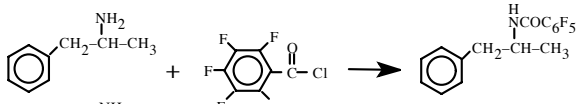
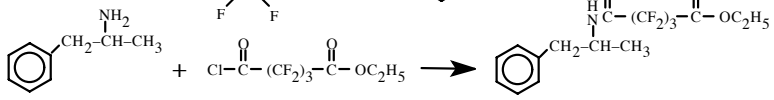
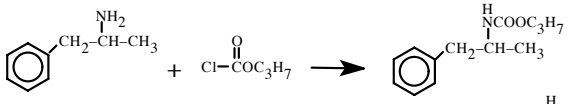
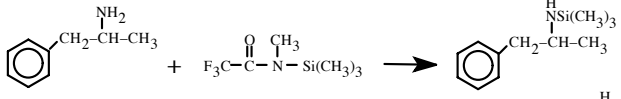
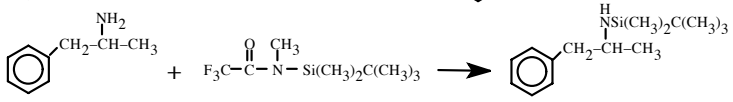
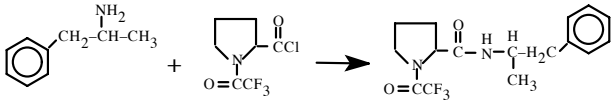
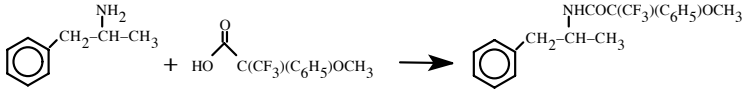
Table 1. (Continued)

Reagent and reaction	Characteristics
4-Carbethoxyhexafluorobutyryl chloride (4-CB) 	Form stable products with secondary amines, such as methamphetamine, allowing the removal of excess agent by adding protic solvents.
(S)-(–)-*N*-(Trifluoroacetyl)-prolyl chloride (*l*-TPC) 	Widely used for amine drugs; With a proton at the chiral center in α-position to the carbonyl group, storage and reaction conditions have to be carefully controlled to avoid racemization through keto-enol tautomerization.
Propyl chloroformate 	Fast reaction and the resulting derivatives are water soluble allowing the removal of by-products through aqueous washing
(–)-α-Methoxy-α-trifluoromethylphenylacetic acid (MTPA) 	More effective than *l*-TPC in resolving ephedrines and in generating ions for designating these analytes and their isotopically labeled internal standards.
Alkylation	
DMF-Dialkylacetal (n = 1, 2, 3, or 4) 	Most commonly used for carboxyl groups, but also reacts with amine, phenol, and amino acid; With n = 1, 2, 3, or 4 to control analyte retention time.
Trimethylanilinium hydroxide (TMAH) 	Commonly used as a flash alkylation reagent.
Tetrabutylammonium hydroxide (TBH) 	Especially suitable for low molecular weight amines.
BF_3/Methanol (*n*-Butanol) (n = 1 or 4) 	Most commonly used to form methyl (butyl) ester with acid.

[a] Information included in this column are only for general reference purpose and not meant to be comprehensive nor critical evaluation.
[b] TFAA, PFPA, HFBA, TCAA, and AA are trifluoroacetic, pentafluoropropionic, heptafluorobutyric, trichloroacetic, and acetic anhydrides.

with different derivatization groups. These CD products were then analyzed by GC-MS and the resulting MS data are hereby presented in two forms: (a) systematic presentation of full-scan spectra; and (b) tabulation of CC data of ions with potential for designating the ISs and analytes. Many (if not most) of these full-scan spectra are not yet available in the literature; their systematic presentation accompanied by CC data should be of daily reference value to forensic and clinical laboratories that are engaged in the analysis of these drugs and metabolites. The CC data should save enormous amounts of time and efforts for practicing laboratories in their search for this analytical parameter to establish an optimal protocol for quantification.

Table 2. Procedure adapted for the derivatizations included in this study

Der. group[a]	Equation
Acetyl	
TCA	
TFA	
TFA/*t*-BDMS	
PFP	
PFP/*t*-BDMS	
HFB	
HFB/*t*-BDMS	
PFB	
4-CB	
Propylformyl	
TMS	
t-BDMS	
l-TPC	
l-MTPA	

[a] TCA: trichloroacetyl; TFA: trifluoroacetyl; PFP: pentafluoropropionyl; HFB: heptafluorobutyryl; PFB: pentafluorobenzoyl; 4-CB: 4-carboethoxyhexafluorobutyryl; *t*-BDMS: *t*-butyldimethylsilyl; TMS: trimethylsilyl; *l*-TPC: (S)-(–)-*N*-(trifluoroacetyl)-prolyl; *l*-MTPA: (–)-α-methoxy-α-trifluoromethylphenylacetyl.

Limitations

As mentioned above, the premise of this work is (a) the systematic presentation of full-scan mass spectra of the analytes and their isotopically labeled analogs in various derivatization forms and (b) the evaluation of ions that may potentially be used for selected ion monitoring in targeted compound analysis protocols. Other aspects (such as those listed below) that may be important to the selection of the most desirable derivatization method for a specific application are not the focus of this study and may not be adequately addressed:

- Availability of adequate number of high-mass ions with unique fragments including part of the analyte (*see* [41] for details);
- Chromatographic characteristics of the resulting derivatives that may provide the optimal resolution between the analytes and interfering compounds in the specific analytical system of interest;
- Yield of the derivatization reaction and the stability of the resulting CD product; and
- Safety issues related to the reagent, reaction condition, and by-products to the analyst and the follow-up analytical system.

I. CHEMICAL DERIVATIZATION

Gas chromatographic methods of analysis have had a long history of application in various areas of the analytical sciences. Since CD is an integral part in these applications, a very significant number of publications addressing various aspects of CD have been accumulated in the literature. For example, there is comprehensive coverage in book format [32,61,76] and articles with narrower scope on individual or a limited number of CD approaches, including the following derivatization groups: acetyl [3,4,18,67,75], TCA [27,39,70], TFA [14,17,22,30,34,50,54,65,67,71,77,79,82,86], TFA/*t*-BDMS [19,62], PFP [23,24,31,39,53,54,59,67,79,84], PFP/*t*-BDMS [19,62], HFB [1,9,10,11,12,13,14,20,25, 28,38,63,64,67,74,79,80,87], HFB/*t*-BDMS [19,62], PFB [2,33,35,37,45,66,72,73,88], 4-CB [15,74,79,85,87], propylformyl [47,56,57,78], TMS [16,18,39,54,55,58,67, 68,69], *t*-BDMS [48], *l*-TPC [6,7,8,11,12,13,16,20,21,25, 26,40,43,46,52,55,60,64,80,81,83,84], and *l*-MTPA [36,49,51,60,68,83]. (*See* **Table 3** for the abbreviations of these derivatization groups.)

A. Standards and Reagents

The following standards (analytes and their respective ISs) used in this study were in 1 mg/mL (or 100 μg/mL) methanolic solution and were purchased from Cerilliant Corp. (Austin, TX): AM, AM-d_5 (ring), AM-d_5 (side chain), AM-d_6, AM-d_8, AM-d_{10}, AM-d_{11}; MA, MA-d_5, MA-d_8, MA-d_9, MA-d_{11}, MA-d_{14}; PPA, PPA-d_3; 1S,2R-(+)-ephedrine, 1S,2R(+)-ephedrine-d_3; MDA, MDA-d_5; MDMA, MDMA-d_5; MDEA, MDEA-d_5, MDEA-d_6; MBDB, MBDB-d_5.

The following CD reagents were purchased from Pierce Chemical Co. (Rockford, IL): *N*-methyl-*N*-trimethylsilyltrifluoro acetamide (MSTFA), *N,O*-bis(trimethylsilyl)-trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (TMCS), *N*-methyl-*N*-(*t*-butyl-dimethylsilyl)-trifluoroacetamide (MTBSTFA) with 1% *t*-butyldimethylchlorosilane (*t*-BDMCS), trimethylchloro-silane (TMCS), *N*-trimethylsilylimidazole (TMSI), trifluoroacetic anhydride (TFAA), pentafluoropropionic anhydride (PFPA), heptafluorobutyric anhydride (HFBA), *N*-propyl chloroformate (PC). 2,3,4,5,6-Pentafluoroben-zoyl chloride was obtained from Acros Organics (Geel, Belgium). 4-Carboethoxyhexafluorobutyryl chloride (4-CB) was purchased from PCR (Gainesville, FL). Chiral CD reagents, (–)-α-methoxy-α-trifluoromethylphenyl-acetic acid (*l*-MTPA) and (S)-(–)-*N*-(trifluoroacetyl)-prolyl chloride (*l*-TPC), were purchased from Aldrich (St. Louis, MO). All other chemicals and solvents were HPLC grade.

B. Derivatization Procedures

Derivatization groups attached to the analyte and IS are listed in the first column of Table 3. Descriptions of CD procedures are summarized in the second column of the table. Drugs/metabolites and ISs included in this study were derivatized using these procedures and then subjected to GC-MS analysis (*see* Section II).

The reagent, protocol, and conditions hereby adapted are not necessarily the optimal ones. They were merely used to produce the derivatives to generate the mass spectrometric information (full-scan spectra and SIM data) for evaluation. The reference cited in the last column (Table 3) merely reflects where the specific CD procedure was found. More comprehensive lists of references involving each specific CD group were provided at the beginning of this section (Section I).

II. GC-MS ANALYSIS

A. Instrumentation and Analytical Parameters

GC-MS analysis was performed on an Agilent 6890 GC interfaced to an Agilent 5973 MS (Agilent: Palo Alto, CA). A 12-m HP-ULTRA-1 crosslinked 100% methyl siloxane capillary column (0.20-mm ID, 0.33-

Table 3. Procedure adapted for the derivatizations of amphetamines

Der. group [a]	Procedure	Ref.
Acetyl	To a 16×100 mm glass tube, add 5 μL analyte (1 mg/mL in methanol) or 50 μL internal standard (0.1 mg/mL in methanol). Evaporate the solvent to dryness under a stream of nitrogen at 50 °C. Add 0.5 mL acetic anhydride and 0.2 mL pyridine. Cap the tube, mix, and incubate for 20 min at 80 °C in a heating block. Cool the mixture and evaporate to dryness under a stream of nitrogen at 50 °C. Reconstitute with ethyl acetate for GC-MS analysis.	[3,4,18,67,75]
TCA	To the dried analyte (*see* the procedure for "Acetyl" shown above) add 150 μL 0.1 mg/mL dimethylaminopyridine (in acetone) and 75 μL trichloroacetic anhydride, then vortex-mixed for approximately 30 s. Wash the derivatized specimens with a solution of water, 1.5-M carbonate buffer (pH 9.5), and 1-N NaOH (1 : 0.5 : 0.4 by volume). Cap the tubes, vortex-mixed for 30 s, then incubate for 45 min at 60 °C in a heating block. Cool the mixture, then centrifuge for 5 min. Freeze the lower aqueous phase and decant the organic phase to a clean tube and evaporate to dryness under a stream of nitrogen at 50 °C. The residue was reconstituted with ethyl acetate for GC-MS analysis.	[27,39,70]
TFA	To the dried analyte (*see* the procedure for "Acetyl" shown above) add 100 μL TFAA. Cap the tube, mix, and incubate for 20 min at 80 °C in a heating block. Cool the mixture and evaporate to dryness under a stream of nitrogen at 50 °C. Reconstitute with ethyl acetate for GC-MS analysis.	[14,17,22,30,34,50, 54,65,67,71,77,79, 82,86]
t-BDMS	To the dried analyte (*see* the procedure for "Acetyl" shown above) add 50 μL acetonitrile and 50 μL MTBSTFA with 1% TBDMCS. Cap the tube, mix, and incubate for 20 min at 90 °C in a heating block. Cool the mixture for GC-MS analysis.	[48]
TFA/*t*-BDMS	Follow the TFA to the point where the product is dried, then proceed with the *t*-BDMS procedure	[19,62]
PFP	Same as the procedure for TFA, except the reagent (PFPA)	[23,24,31,39,53,54, 59,67,79,84]
PFP/*t*-BDMS	Follow the PFP to the point where the product is dried, then proceed with the *t*-BDMS procedure	[19,62]
HFB	Same as the procedure for TFA, except the reagent (HFBA)	[1,9–14,20,25,28, 38,63,64,67,74,79, 80,87]
HFB/*t*-BDMS	Follow the HFB to the point where the product is dried, then proceed with the *t*-BDMS procedure	[19,62]
PFB	To the dried analyte (*see* the procedure for "Acetyl" shown above) add 100 μL acetone and 100 μL PFBC and 1 mL 1-chlorobutane. Cap the tube, mix, and incubate for 30 min in a heating block at 80 °C. Cool the mixture then evaporate to dryness under a tream of nitrogen at 50 °C. Reconstitute the residue with ethyl acetate for GC-MS analysis.	[2,33,35,37,45,66, 72,73,88]
4-CB	To the dried analyte (*see* the procedure for "Acetyl" shown above) add 200 μL of 4-CB solution (1:100 in 1-chlorobutane, v/v, prepared fresh daily). Cap the mixture, vortex-mixed, and incubate for 30 min at 50–60 °C. Convert excess acid chloride to diethyl ester by adding 0.3 mL of anhydrous ethanol, vortex-mixed, and incubate for 30 min at 50–60 °C. Carefully evaporate to dryness (to avoid evaporative loss of derivatives). Reconstitute the residue with ethyl acetate for GC-MS analysis.	[15,74,79,85,87]
Propylformyl	Same as the procedure for TFA, except the reagent (propyl chloroformate).	[47,56,57,78]
TMS	To the dried analyte (*see* the procedure for "Acetyl" shown above) add 100 μL MSTFA. Cap the tube, mix, and incubate for 20 min at 90 °C in a Dry-bath heating block. Cool the mixture for GC-MS analysis.	[16,18,39,54,55,58, 67–69]
l-TPC	To a 16×100 mm glass tube, added 5 μL analyte (1 mg/mL in methanol) or 50 μL internal standard (0.1 mg/mL in metanol). Add 0.5 mL saturated potassium carbonate, 4 mL *n*-hexane and 50 μL *l*-TPC[b]. Mix for 10 min on a shaker, then centrifuge at 3000 rpm for 5 min. Freeze the lower aqueous phase and decant the upper layer to a clean tube and evaporate to dryness under a stream of nitrogen at 50 °C. Reconstitute the residue with ethyl acetate for GC-MS analysis.	[6–8,11–13,16,20, 21,25,26,40,43,46, 52,55,60,80,81,83, 84]
l-MTPA	To the dried analyte (*see* the procedure for "Acetyl" shown above) add 50 μL *N,N*-dicyclohexycarbodiimide and 100 μL *l*-MTPA[b]. Cap the tube, thoroughly mixed, and incubate at 70 °C for 20 min. Cool the mixture, then evaporate to dryness under a stream of nitrogen at 50 °C. Reconstitute the residue with ethyl acetate for GC-MS analysis.	[36,49,51,60,68,83]

[a] *See* Table 2 for the abbreviations of the derivatization groups.
[b] *l*-TPC: (S)-(–)-*N*-(trifluoroacetyl)-prolyl chloride; *l*-MTPA: (–)-α-methoxy-α-trifluoromethylphenylacetic acid.

μm film thickness) from Agilent (Wilmington, DE) was used for this study. Helium carrier gas flow rate was 1.0 mL/min. The injector and GC-MS interface temperatures were maintained at 250 and 280 °C, respectively. Various GC oven temperature and programming parameters were adapted for the analyses of derivatized analytes and their ISs. Because chromatographic resolution was not the emphasis of this study, temperature and programming rates were not critical parameters and will not be provided with details.

B. Collection of Mass Spectrometric Data

Typically, a full-scan mass spectrum of the drugs/metabolites of interest was obtained by injecting the CD product into the GC-MS system. With few exceptions, full-scan mass spectra were collected starting at *m/z* 40 or 50 and ended at a mass higher than the molecular weights of the derivatized products.

The drug/metabolite and its corresponding IS were analyzed separately. Information derived from these ion chromatograms (retention time and MS data) was used to characterize the analytes and their ISs. Full-scan MS data from these two runs were reviewed to select ions that may be suitable for the designations of the analytes and the ISs in routine GC-MS protocols.

The same CD products were injected (separately) into the GC-MS using selected ion monitoring (SIM) mode. Ions selected from the full-scan MS data for both the analyte and the IS were monitored. Mass spectrometric data derived from these SIM runs were then used to evaluate the CC data (an analyte's contribution to the intensities of ions designated for its isotopic analog, and vice versa). Details of the methodology have been described in our earlier publications [39,41].

Full-scan mass spectra were stored as digital data and were then converted (DeltaGraph: Seattle, WA) into mass spectra of a more desirable format as shown in Section III.

III. FULL-SCAN MASS SPECTRA (*SEE* APPENDIX I)

Two sets of data (full-scan mass spectra and CC data) were collected and included in this report. Both sets of data include various CD products of the drugs/metabolites (Table 3) along with their commercially available isotopically labeled analogs (ISs).

Cross-contribution data will be presented in Section IV and will be described later. The full-scan mass spectra are presented as figures (*see* Appendix I). These figures are organized as described below. All mass spectra resulting from the use of one CD reagent for a specific analyte and all of this analyte's isotopic analog(s) are shown in one figure. For example, **Figure 1-A** includes the full-scan mass spectra of the underivatized AM, AM-d_5 (ring), AM-d_5 (side chain), AM-d_6, AM-d_8, AM-d_{10}, AM-d_{11}. Corresponding mass spectra of acetyl-derivatized AM are shown in **Figure 1-B**. Mass spectra of the other compounds (MA, PPA, ephedrine, MDA, MDMA, MDEA, MBDB and their isotopic analogs) are shown in **Figures 2–8**. The molecular weights shown in these figures were cauculated based on the information shown below: H, 1.00794; D, 2.01400; C, 12.0107; ^{13}C, 13.00335; N: 14.00674; O, 15.99940; F, 18.99840; Si, 28.08550; Cl, 35.4527.

To the best of our knowledge, many (if not most) of these mass spectra are not published in literature generally available to the scientific community. Certainly, they have not been systematically compiled as presented here and, therefore, should be of daily reference value to laboratories engaged in drug analysis.

IV. ION INTENSITY CROSS-CONTRIBUTION DATA (*SEE* APPENDIX II)

In addition to the full-scan mass spectra shown in Section III, CC data presented in this section are based on data collected using SIM. These are pairs of ions with the potential to designate the drugs/metabolites and their isotopic analogs when the latter are used as the IS in quantitative GC-MS analysis protocols.

The CC data may be irrelevant in cases where the number of the deuterium atoms in the isotopically labeled analogs is so large that the analytes and the internal standards are practically chromatographically resolved. However, these analogs (such as methamphetamine-d_{14}) are still included in this study for the following two reasons: (a) to optimize the analytical time and to keep the system clean, chromatography is normally conducted at high temperatures where adequate resolution between the analyte and the internal standard is unlikely; (b) the retention time window set for automatic integration of ion intensities may not always be properly adjusted.

As briefly mentioned in the last section, full-scan mass spectra data were used to select potential ion-pairs. These ions were then included in the SIM data collection process. Cross-contribution data were calculated based on data derived from SIM runs. As footnoted in **Tables 4–11** (*see* Appendix II), only ion-pairs with <5% CC are listed. Common practices in choosing the linear model for calibration deem the use of ion-pairs with higher CC inappropriate for quantification (or as a criterion for qualitative confirmation purpose). This is especially true when the calibration is to be established for a reasonable

concentration range (e.g., in 2 orders of magnitude). Besides, full-scan mass spectra show this relatively well when the CC is ≥5%.

The sequence and manner adapted to present CC data are different from that adapted for presenting the full-scan mass spectra. Specifically, these data are presented in table format and each table includes the data derived from the use of one specific isotopic analog (IS), but includes all CD products. For example, **Table 4-A** includes the CC data resulting from the use of AM-d_5 (ring) as the IS for the analysis of AM. This table includes all data resulting from the use of the following derivatization groups: none, acetyl, TCA, TFA, TFA/*t*-BDMS, PFP, PFP/*t*-BDMS, HFB, HFB/*t*-BDMS, PFB, 4-CB, propylformyl, TMS, *t*-BDMS, *l*-TPC, and *l*-MTPA. Corresponding data derived from the use of AM-d_5 (side chain), AM-d_6, AM-d_8, AM-d_{10}, AM-d_{11}, as the IS, are shown in **Tables 4-B** to **4-F**. Similar data for MA, PPA, ephedrine, MDA, MDMA, MDEA, and MBDB are presented in **Tables 5–11**, respectively.

Since optical isomers were resolved when chiral derivatization reagents (*l*-TPC and *l*-MTPA) were used, CC data are listed in two pairs. Specifically, these are CC data for the *d*-form of the analytes against the *d*-form of their ISs and the *l*-form of the analytes against the *l*-form of their ISs.

As shown in **Tables 4–11**, the quality of the ion-pairs that may be selected to designate a specific analyte and a specific isotopically labeled analog varies with the CD methods. On the other hand, using a specific CD method, the quality of the resulting ion-pairs varies with the isotopically labeled analogs. Therefore, the ion-pair with the highest quality, which should be selected for a quantitative analysis process, varies with the IS and the CD used in the protocol. Thus, the CC data tabulated in **Tables 4–11** should save an enormous amount of time and effort for practicing laboratories in their search for this analytical parameter to establish an optimal protocol for quantification.

SUMMARY

Following a review of CD methods for amine drugs and a search of commercially available isotopically labeled analogs (of these drugs), the authors carried out CD reactions and performed GC-MS analysis of these CD products. Full-scan mass spectra of these drugs/metabolites and their isotopic analogs in various CD forms are systematically presented. Most of these mass spectra are not available in the open literature and should be of daily reference values to clinical and forensic laboratories that are engaged in drug analysis.

Full-scan MS data were further used to select ion-pairs that have potential for designating the drugs/metabolites and their ISs in quantitative analysis protocols. The CC data of these ion-pairs were evaluated using data collected under the SIM mode and summarized in table format. These data should save an enormous amount of time and effort for practicing laboratories in their search for this analytical parameter to establish optimal protocols for quantification.

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