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A derivatisation agent selection guide†

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The study reported herein is aimed at the greenness assessment of 267 derivatisation agents that are frequently applied in analytical chemistry and related disciplines. Multicriteria decision analysis allowed obtaining three rankings of derivatisation agents applied in liquid chromatography, gas chromatography and chiral analysis. The criteria of assessment included the safety information obtained from material safety data sheets and physicochemical and environmental parameters predicted with relevant models. As for some of the agents predicted data were not available, these agents were assessed with a smaller number of criteria, within the ranking of low confidence. The results of the study will help to apply greener derivatisation agents, wherever the green chemistry principle of avoiding derivatisation cannot be fulfilled.

1. Introduction

The development of new tools for providing high quality information in a cost-effective and expeditious way is one of the main aims of analytical chemistry. Remarkably, the introduction of the 12 principles of green chemistry[1] paved the way forward for the development of analytical methodologies that are, ideally, inherently safe for the operator and the environment, with the least possible consumption of energy and chemicals, and minimum generation of wastes.[2,3] Thus, green aspects are increasingly being considered besides the main features of analytical methods such as accuracy, sensitivity, selectivity and precision.[3] In this way, both "3R" (reduction, replacement and recycling)[4] and "4S" (specific methods, smaller dimensions, simpler methods and statistics)[5] approaches have been reported in the literature towards greener analytical methodologies.[2]

The removal, replacement by greener alternatives or minimisation of reagents and solvents used in chemical processes is recommended in several of the 12 principles of green chemistry.[1] While certain strategies have enabled reagentless and solventless processes, many scientific and technological activities require significant amounts of both solvents and chemicals. In the latter case, selection of solvents and chemicals with little (or none) environmental, health and safety (EHS) issues is highly recommended. In this sense, a number of solvent selection guides have been developed in recent years, enabling the selection of greener alternatives to harmful solvents typically used in scientific and technological processes.[6–14] The possibility of developing reagent selection guides has been however much less explored, probably due to the additional EHS issues associated with these non-inert chemicals and lack of physicochemical data, among other aspects.[8] Notwithstanding the above, both Pfizer and GSK have made remarkable efforts towards the selection of greener reagents among the ones used in common transformations by the pharmaceutical industry.[15–17] Specifically, Alfonsi *et al.*[8] first introduced the concept of a reagent guide almost one decade ago and, more recently, scientists at GSK developed a selection guide for reagents used in a wide range of transformations in the pharmaceutical industry,[16] as well as a selection guide for greener acids and bases.[17] Even though the above mentioned guides cover a broad range of chemicals used in medicinal chemistry and the pharmaceutical industry, further progress is necessary to provide valuable information to other fields where derivatisation reactions are required.

Multicriteria decision analysis (MCDA) consists of a set of tools for solving complex decision problems. A result of the analysis of a dataset of alternatives, described by criteria, is a selection of the first preference solution and creation of the full ranking of the remaining alternatives. MCDA has been applied in sustainability assessments[18] and environmental managerial processes.[19] More specifically, MCDA has been used to rank solvents according to their greenness[12] and environmental risks related to their emissions.[13] Other chemical assessment applications include screening amine-based solvents for CO_2 capture[20] or screening of more sustainable substitutes for chemicals, based on the quantitative structure–use relationship.[21]

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The term derivatisation refers to a chemical reaction that aims to change the chemical structure of target compounds and, as a consequence, obtain derivatives with desirable physicochemical properties for separation and/or detection. Ideally, derivatisation should be quantitative and selective, and fast and simple to perform. The 8th principle of green chemistry states that unnecessary derivatisation should be minimised or avoided whenever possible in order to avoid or minimise reagent consumption and the corresponding waste generation.[1] Thus, a widely employed strategy in synthetic organic chemistry such as the use of blocking or protecting groups (or any temporary modifications) should be avoided to reduce its impact on the process mass intensity. Even though the complete removal of derivatisation agents is the ideal solution, it should be borne in mind that their use in analytical chemistry has enabled the determination of a wide range of compounds not directly amenable to analysis, among other performance benefits. Particularly, analytical derivatisation can enhance detection and separation, extractability, thermal stability, selectivity, and the overall quality of the data.[22–24] Thus, a wide range of disciplines, *e.g.*, chemical, biochemical, medical, forensic and environmental sciences, make use of analytical derivatisation.[22,23] Selection of greener derivatisation agents would therefore help in the development of less harmful methodologies where derivatisation reactions cannot be avoided.

The work reported herein focuses on the development of a reagent selection guide to rank derivatisation reagents relevant to analytical chemistry and related disciplines taking into account their EHS concerns. We believe that the greenness assessment of derivatisation agents performed in this work will help to focus future efforts in the replacement of the chemicals which show major issues by greener alternatives.

2. Materials and methods

2.1. Data collection

The dataset describing commercially available derivatisation agents (n = 267) was created (see the ESI†). Each derivatisation agent was described by 13 assessment criteria as presented in Table 1. The data were taken from material safety data sheets (MSDS) of the respective compounds and from modelling results available at ChemSpider webpage.[25] Derivatisation agents were divided into three subsets, according to their area of application, namely liquid chromatography (LC) derivatisation agents (n = 133), gas chromatography (GC) derivatisation agents (n = 98) and chiral derivatisation agents (n = 36). This grouping was based on statements "for LC derivatisation", "for GC derivatisation" or "for chiral derivatisation" from the Sigma-Aldrich web page.

The required data for some of the evaluated derivatisation agents were not available on the ChemSpider web page. Rankings of lower confidence were thus prepared in order to include them in the assessment procedure. High confidence rankings were prepared on the basis of all criteria presented in Table 1. Low confidence rankings were based on hazard statements, precautionary statements, carcinogenicity, signal wording and special hazards arising from the substance or mixture/hazardous decomposition products criteria.

2.2. Assessment criteria

The sources of the data of the respective criteria are listed in Table 2. The application of MCDA tools requires defining preference functions for every single criterion. They are usually defined as "the higher the better" or "the lower the better". The first preference function was applied for the boiling point, flash point and total removal by wastewater treatment. The rest

Table 1 Criteria used to perform rankings. Weights in brackets are for low confidence ranking

Criterion	Description	Weight
Boiling point	From the ChemSpider web page. Experimental data were taken if available.	0.025
Flash point	If not, data predicted by ACD/Labs or EPISuite models were applied	0.025
Vapour pressure		0.025
log K_{OW}		0.025
log K_{OC}		0.025
log BCF		0.025
Total removal by wastewater treatment (%)		0.025
Persistence time		0.025
Hazard statements (H)	From MSDS, SECTION 2: Hazards identification, 2.2 Label elements. For translation of statements to numerical values see Table 2	0.25 (0.3125)
Precautionary statements (P)	From MSDS, SECTION 2: Hazards identification, 2.2 Label elements. For translation of statements to numerical values see Table 3	0.2 (0.25)
Carcinogenicity (IARC)	From MSDS, SECTION 11: Toxicological information, information on toxicological effects. Group 2A: Probably carcinogenic to humans – 3 points; not identified as a probable, possible or confirmed human carcinogen – 0 points	0.05 (0.625)
Signal word	From MSDS, SECTION 2: Hazards identification, 2.2 Label elements. "None" – 0 points, "Warning" – 1 point, "Danger" – 4 points	0.2 (0.25)
Special hazards arising from the substance or mixture/hazardous decomposition products	From MSDS, SECTION 5: Firefighting measures, 5.2 Special hazards arising from the substance or mixture, SECTION 10: Stability and reactivity, 10.6 Hazardous decomposition products. For translation of statements to numerical values see Table 4	0.1 (0.125)

Table 2 Descriptions of the hazard statements and their translation to penalty points

	Description	Points
H224	Extremely flammable liquid and vapour	9
H225	Highly flammable liquid and vapour	7
H226	Flammable liquid and vapour	5
H228	Flammable solid	3
H242	Heating may cause a fire	3
H251	Self-heating; may catch fire	3
H261	In contact with water releases flammable gas	2
H280	Contains gas under pressure; may explode if heated	2
H290	May be corrosive to metals	2
H300	Fatal if swallowed	10
H301	Toxic if swallowed	7
H302	Harmful if swallowed	5
H304	May be fatal if swallowed and enters airways	8
H310	Fatal in contact with skin	10
H311	Toxic in contact with skin	7
H312	Harmful in contact with skin	5
H314	Causes severe skin burns and eye damage	5
H315	Causes skin irritation	2
H317	May cause an allergic skin reaction	2
H318	Causes serious eye damage	7
H319	Causes serious eye irritation	5
H330	Fatal if inhaled	10
H331	Toxic if inhaled	7
H332	Harmful if inhaled	5
H334	May cause allergy or asthma symptoms or breathing difficulties if inhaled	3
H335	May cause respiratory irritation	2
H336	May cause drowsiness or dizziness	2
H341	Suspected of causing genetic defects	7
H350	May cause cancer	10
H351	Suspected of causing cancer	7
H360	May damage fertility or the unborn child	10
H361	Suspected of damaging fertility or the unborn child	7
H370	Causes damage to organs	10
H372	Causes damage to organs through prolonged or repeated exposure	8
H373	May cause damage to organs through prolonged or repeated exposure	7
H400	Very toxic to aquatic life	10
H410	Very toxic to aquatic life with long-lasting effects	10
H411	Toxic to aquatic life with long-lasting effects	10
H412	Harmful to aquatic life with long-lasting effects	7
H413	May cause long-lasting harmful effects on aquatic life	5

of the criteria were evaluated according to "the lower the better" preference function.

MCDA methods offer the possibility to assign different relative importance to the respective criteria in the form of weights. In high confidence rankings, low weights were given to criteria referring to physicochemical parameters, persistence time and removal during wastewater treatment. These data are mostly predicted by models, so their reliability is lower than that of measured values. These criteria mostly characterise risks related to the environmental fate of chemicals, not the exposure or occupational risks. The data that are available in MSDS are given higher weights as these criteria directly reflect the risks connected with the application of derivatisation agents. Here, hazard statements, precautionary statements and signal wording characterise application risks. Carcinogenicity is given smaller weight as this criterion presents little variability, since only 2 derivatisation agents are considered possible human carcinogens. For low confidence ranking, the ratios between weights remained unchanged in comparison with high confidence ranking.

The data being input to TOPSIS (Technique for Order of Preference by Similarity to Ideal Solution) must be in the form of numerical values. Therefore, hazard statements and precautionary statements were transformed to penalty points in 10 point scales. Points for hazard statements are presented in Table 2. Ten points were given to hazard statements with zero pass and first pass red flags as presented in a recently proposed unified metrics toolkit for the assessment of the sustainability of reactions.[26] First pass amber flags statements from this assessment were given seven points in our study. Red and amber flags statements are marked in Table 2 with appropriate colours. The rest of the statements got penalty points according to the risks related to their descriptions. Derivatisation agents with multiple hazard statements got their points summed up to obtain a final numerical value of this criterion.

Points for precautionary statements are presented in Table 3. The points for this criterion were given to the respective statements in a similar way to the case of hazard statements according to their risks. The points for derivatisation agents with multiple precautionary statements were summed up to obtain a numerical value of this criterion.

Signal wording transformation to obtain numerical values, "none" – 0 points, "warning" – 1 point, "danger" – 4 points, was also used in the transformation of "special hazards arising from the substance or mixture/hazardous decomposition products" into numerical values, as shown in Table 4. Following the approach of the analytical eco-scale,[27] the points for signal wording were multiplied by the number of labelling pictograms. For compounds with (+) indication, extra 10 points were given as these compounds are characterised by hazards with lethal effects. For multiple compounds formed during fire or decomposition, their points were summed up to obtain the final value of the criterion.

2.3. TOPSIS analysis

The algorithm of TOPSIS requires few simple steps to calculate the final ranking. The step one is to normalize the input data to form a "normalised decision matrix". Normalised value r_{xy} is calculated according to the equation:

$$r_{xy} = x_{xy} \div \sqrt{\sum_{x-1}^{m} x_{xy}^2}, \quad x = 1, 2, \ldots, m \text{ and } y = 1, 2, \ldots, n, \quad (1)$$

where x_{xy} and r_{xy} are the original and normalised scores in the decision matrix, respectively.

Then, the weighted normalised decision matrix is calculated. The weighted normalised values v_{xy} are calculated according to the equation:

$$v_{xy} = r_{xy} \times w_y \quad x = 1, 2, \ldots, m \text{ and } y = 1, 2, \ldots, n, \quad (2)$$

where w_y is the weight of the criterion and $\sum_{y=1}^{n} w_y = 1$. In this study, the applied weights are presented in Table 1.

Table 3 Descriptions of the precautionary statements and their translation to penalty points

Precautionary statement (P)	Description	Points
P201	Obtain special instructions before use	10
P210	Keep away from heat/sparks/open flames/hot surfaces – no smoking	3
P231	Handle under inert gas	7
P232	Protect from moisture	3
P233	Keep the container tightly closed	3
P235	Keep cool	3
P260	Do not breathe dust/fume/gas/mist/vapours/spray	7
P261	Avoid breathing dust/fume/gas/mist/vapours/spray	5
P264	Wash hands thoroughly after handling	3
P273	Avoid release to the environment	10
P280	Wear protective gloves/protective clothing/eye protection/face protection	5
P284	Wear respiratory protection	10
P301	IF SWALLOWED:	5
P302	IF ON SKIN:	6
P303	IF ON SKIN (or hair):	7
P304	IF INHALED:	10
P305	IF IN EYES:	7
P308	IF exposed or concerned:	5
P310	Immediately call a POISON CENTER or doctor/physician	10
P311	Call a POISON CENTER or doctor/physician	7
P312	Call a POISON CENTER or doctor/physician if you feel unwell	3
P313	Get medical advice/attention	2
P330	Rinse mouth	5
P331	Do NOT induce vomiting	5
P337	If eye irritation persists:	5
P338	Remove contact lenses, if present and easy to do. Continue rinsing	5
P340	Remove the victim to fresh air and keep at rest in a position comfortable for breathing	3
P342	If experiencing respiratory symptoms:	7
P350	Gently wash with plenty of soap and water	3
P351	Rinse cautiously with water for several minutes	3
P352	Wash with plenty of soap and water	3
P353	Rinse skin with water/shower	3
P361	Remove/take off immediately all contaminated clothing	3
P370	In case of fire:	7
P378	Use ... for extinction	5
P391	Collect spillage	5
P403	Store in a well-ventilated place	3
P405	Store locked up	2
P410	Protect from sunlight	3
P501	Dispose of contents/container to ...	5

In the next step, positive ideal solution (A^*) and negative ideal solution (A^-) are calculated with the following equations:

$$A^* = \{(\max_x v_{xy} | y \in C_b), (\min_x v_{xy} | y \in C_c)\} = \{v_y^* | y = 1, 2, ..., m\} \text{ and} \quad (3)$$

$$A^- = \{(\min_x v_{xy} | y \in C_b), (\max_x v_{xy} | y \in C_c)\} = \{v_y^- | y = 1, 2, ..., m\}. \quad (4)$$

The separation measures using the m-dimensional Euclidean distance are determined in the next step. The separation measures of each alternative from the positive (S_x^*) and negative (S_x^-) ideal solutions, respectively, are calculated as follows:

$$S_x^* = \sqrt{\sum_{y=1}^{m} \left(v_{xy} - v_y^*\right)^2} \; y = 1, 2, \ldots, m \text{ and} \quad (5)$$

$$S_x^- = \sqrt{\sum_{y=1}^{m} \left(v_{xy} - v_y^-\right)^2} \; y = 1, 2, \ldots, m. \quad (6)$$

Then the relative distance to the ideal solution is calculated. The relative distance of the alternative A_x with respect to A^* is defined as:

$$C_x^* = \frac{S_x^-}{S_x^* + S_x^-}, \quad x = 1, 2, \ldots, m \text{ and } 0 < C_x^* < 1. \quad (7)$$

The alternative with C_x^* closest to 1 is called the best preference. All alternatives are characterised by the values of similarity to the ideal solution and the ranking is obtained. The rankings for all three groups of derivatisation agents are provided in Tables 5–7.

Table 4 Translation of the "special hazards arising from the substance or mixture/hazardous decomposition products" criterion to numerical values

Compounds	No pictograms	Signal wording	Points
Carbon oxides	1	Warning	1
Nitrogen oxides	4	Danger	16
Sulphur oxides	3	Danger	12
Phosphorus oxides	1	Danger	4
Borane/boron oxides	1	Danger	4
Iron oxides	0	0	0
Sodium oxides	2	Danger	8
Silicon oxides	0	0	0
Hydrogen chloride	2	Danger	8
Hydrogen bromide	3	Danger	12
Hydrogen iodide	1	Danger	4
Hydrogen fluoride	2	Danger (+)	18
Hydrogen cyanides	3	Danger (+)	22
Diazomethane	3	Danger	12
Dimethylamine	3	Danger	12

3. Results and discussion

As stated in the above section, derivatisation agents were assessed within three groups. The assessment results for LC, GC, and chiral derivatisation agents are presented in the next three subsections. It should be noted here that the results for derivatisation agents present in the different subsets are incomparable. As the assessment results for high confidence rankings are based on more assessment criteria, it is advisable to consider these results. If not available, low confidence ranking brings approximate information on the performance of derivatisation agents. Another important information is the assessment score, elegantly named "similarity to ideal solution". The value equal to "1" means that all assessment criteria

Table 5 Assessment results of LC derivatisation agents

LC derivatisation agent	CAS number	High confidence rank	High confidence score	Low confidence rank	Low confidence score
(3*R*,4*R*)-2,5-Dioxotetrahydrofuran-3,4-diyldiacetate	6283-74-5	1	0.9291	1	1.0000
2,2′-Dihydroxy-1*H*,1′*H*-2,2′-biindene-1,1′,3,3′(2*H*,2′*H*)-tetrone dihydrate	5950-69-6			1	1.0000
Ferrocenecarboxaldehyde	12093-10-6			1	1.0000
2-Hydroxy-1,2-diphenylethanone	119-53-9	2	0.9256	1	1.0000
2-Acetylbenzaldehyde	24257-93-0	3	0.9252	1	1.0000
9*H*-Fluorene-2-carbaldehyde	30084-90-3	4	0.9190	1	1.0000
1-{[4-(Dimethylamino)benzoyl]oxy}-2,5-pyrrolidinedione	58068-85-2			8	0.9492
Ferrocenecarbonyl azide	1273-85-4			8	0.9492
4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione	4233-33-4	5	0.9107	8	0.9492
4-(Dimethylamino)benzaldehyde	100-10-7	6	0.9076	8	0.9492
(4-Formyl-5-hydroxy-6-methyl-3-pyridinyl)methyl dihydrogen phosphate	41468-25-1	7	0.9009	13	0.9371
2-(Tri-1-pyrrolidinylphosphoranylidene)hydrazinecarboxylic acid-2,5-dioxo-1-pyrrolidinyl ester	1395920-13-4			13	0.9371
Sodium 3,4-dioxo-3,4-dihydro-1-naphthalenesulfonate	521-24-4			13	0.9371
Bis(phenylmethyl)-2-(ethoxymethylidene)propanedioate	56606-21-4			16	0.9356
3-Hydroxy-5-(hydroxymethyl)-2-methylisonicotinaldehyde hydrochloride (1:1)	65-22-5			17	0.9254
1-[2-(4-Nitrophenyl)acetoxy]-2,5-pyrrolidinedione	68123-33-1	8	0.8960	17	0.9254
7-[(2-Aminoethyl)amino]-*N*-[2-(dimethylamino)ethyl]-2,1,3-benzoxadiazole-4-sulfonamide	913253-56-2	9	0.8852	19	0.9139
3-(Bromomethyl)-7-methoxy-2*H*-1,4-benzoxazin-2-one	124522-09-4	10	0.8843	19	0.9139
5-Butyl-2-pyridinecarboxylic acid	536-69-6	11	0.8737	22	0.9014
(6-Bromo-3-pyridinyl)boronic acid	223463-14-7	12	0.8735	21	0.9027
{4-[7-(Diethylamino)-2-oxo-2*H*-chromen-3-yl]phenyl}(oxo)acetonitrile	203256-20-6	13	0.8732	22	0.9014
N,*N*-Dimethyl-5-(1-piperazinylsulfonyl)-1-naphthalenamine	86516-36-1	14	0.8715	26	0.8992
2,5-Dimethyl-1*H*-pyrrole-3,4-dicarboxaldehyde	56139-74-3	15	0.8517	28	0.8699
N,*N*-Dimethylglycine	1118-68-9	16	0.8418	22	0.9014
N-(2-Maleimidoethyl)ferrocenecarboxamide	952102-12-4			22	0.9014
1,2-Benzo-3,4-dihydrocarbazole-9-ethyl-*p*-toluenesulfonate	861881-76-7			27	0.8864
7-Fluoro-2,1,3-benzoxadiazole-4-sulfonamide	91366-65-3	17	0.8410	29	0.8655
7-Fluoro-2,1,3-benzoxadiazole-4-sulfonic acid ammoniate (1:1)	84806-27-9			29	0.8655
2-Methoxy-2,4-diphenyl-3(2*H*)-furanone	50632-57-0	18	0.8288	33	0.8468
2-(4-Isocyanatophenyl)-6-methyl-1,3-benzothiazole	67229-93-0	19	0.8267	31	0.8554
eta5-(1-Aminocyclopentadienyl)(cyclopentadienyl)iron(II)	1273-82-1			32	0.8550
Sodium 4-{2-[(*E*)-2-{(3*E*)-3-{(2*E*)-2-[3,3-dimethyl-1-(4-sulfonatobutyl)-1,3-dihydro-2*H*-indol-2-ylidene]ethylidene}-2-[(4-isothiocyanatophenyl)sulfanyl]-1-cyclohexen-1-yl}vinyl]-3,3-dimethyl-3*H*-indolium-1-yl}-1-butanesulfonate	152111-91-6			35	0.8360
2,3-Naphthalenedicarbaldehyde	7149-49-7	20	0.8140	36	0.8304
1-Pyrenecarbaldehyde	3029-19-4	21	0.8140	36	0.8304
9-Phenanthrylboronic acid	68572-87-2	22	0.8123	38	0.8295
Ferroceneboronic acid	12152-94-2			38	0.8295
9-(Chloromethyl)anthracene	24463-19-2	23	0.8099	41	0.8278
(Bromomethyl)benzene	100-39-0	24	0.8093	42	0.8254
9-Oxo-10(9*H*)-acridineacetic acid	38609-97-1	25	0.8083	43	0.8222
4-Fluoro-7-nitro-2,1,3-benzoxadiazol	29270-56-2	26	0.8082	40	0.8292
2-Methyl-1*H*-isoindole-1,3(2*H*)-dione	550-44-7	27	0.8076	43	0.8222
9-(Diazomethyl)anthracene	10401-59-9			43	0.8222
4,5-Dimethoxy-1,2-benzenediamine dihydrochloride	131076-14-7			43	0.8222
2-Hydrazinopyridine	4930-98-7	28	0.8073	43	0.8222
4-(1-Methylhydrazino)-7-nitro-2,1,3-benzoxadiazole	214147-22-5	29	0.8064	43	0.8222
6-Amino-1*H*-phenalen-1-one	70402-14-1	30	0.8060	43	0.8222
5-(Dimethylamino)-1-naphthalenesulfonohydrazide	33008-06-9	31	0.8052	58	0.8091
9*H*-Fluoren-9-ylmethyl hydrazinecarboxylate	35661-51-9	32	0.8046	43	0.8222
1-(Acridin-9-yl)-1*H*-pyrrole-2,5-dione	49759-20-8	33	0.8043	43	0.8222
1-{[(2,6-Dimethyl-4-quinolinyl)carbonyl]oxy}-2,5-pyrrolidinedione	569355-30-2			43	0.8222
9,10-Phenanthrenediamine	53348-04-2	34	0.8027	53	0.8204
Sodium 9,10-dimethoxy-2-anthracenesulfonate	67580-39-6			54	0.8184
N-(4-Nitrobenzyl)-1-propanamine hydrochloride (1:1)	68133-98-2			55	0.8140
1,3-Benzodioxole-5,6-diamine dihydrochloride	81864-15-5			55	0.8140
2-Chloro-6-[(3-hydroxypropyl)amino]-1*H*-phenalen-1-one	113722-81-9	35	0.7979	55	0.8140
N-Acetyl-3-sulfanyl-D-valine	15537-71-0	36	0.7949	58	0.8091
N,*N*-Dimethyl-7-(1-piperazinyl)-2,1,3-benzoxadiazole-4-sulfonamide	139332-64-2	37	0.7938	58	0.8091
5,5-Dimethyl-1,3-cyclohexanedione	126-81-8	38	0.7909	1	1.0000
4-[(Diethylamino)methyl]benzohydrazide	62642-61-9	39	0.7885	61	0.8068
4-(Diethylamino)benzohydrazide	100139-54-6	40	0.7882	61	0.8068

Table 5 *(Contd.)*

LC derivatisation agent	CAS number	High confidence rank	High confidence score	Low confidence rank	Low confidence score
5-(Chlorosulfonyl)-2-[6-(diethylamino)-3-(diethyliminio)-3*H*-xanthen-9-yl]benzenesulfonate	62796-29-6			63	0.7979
5-(Dimethylamino)-1-naphthalenesulfonyl chloride	605-65-2	41	0.7859	94	0.7232
4′-Phenyl-3*H*,3′*H*-spiro[2-benzofuran-1,2′-furan]-3,3′-dione	38183-12-9	42	0.7754	12	0.9451
Diethyl (ethoxymethylene)malonate	87-13-8	43	0.7709	64	0.7833
2,2-Dihydroxy-1*H*-indene-1,3(2*H*)-dione	485-47-2	44	0.7673	67	0.7767
2-Cyanoacetamide	107-91-5	45	0.7652	68	0.7763
4-(Bromomethyl)-6,7-dimethoxy-2*H*-chromen-2-one	88404-25-5	46	0.7649	65	0.7788
4-(Bromomethyl)-7-methoxy-2*H*-chromen-2-one	35231-44-8	47	0.7642	65	0.7788
5-Methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one	89-25-8	48	0.7626	68	0.7763
(1*R*,2*S*)-1,2-Bis(4-methoxyphenyl)-1,2-ethanediamine	58520-45-9	49	0.7617	68	0.7763
4-Nitro-7-(1-piperazinyl)-2,1,3-benzoxadiazole	139332-66-4	50	0.7616	68	0.7763
3,3′-[(1*E*,2*E*)-1,2-Hydrazinediylidenedi(*E*)methylylidene]diphenol	18428-76-7	51	0.7585	68	0.7763
Carbamodithioic acid, *N*,*N*-diethyl-, sodium salt, hydrate (1:1:3)	20624-25-3			73	0.7632
3′,6′-Dihydroxy-5-isothiocyanato-3*H*-spiro[2-benzofuran-1,9′-xanthen]-3-one	27072-45-3	52	0.7557	74	0.7625
1-[4-(Aminomethyl)phenyl]pyridinium chloride	1459205-36-7			75	0.7556
N-Ferrocenyl-maleimide	96483-68-0			76	0.7472
1,1″-[Oxybis(3-oxo-3,1-propanediyl)]bis-ferrocene	132098-76-1			76	0.7472
4-[(*E*)-(4-Isothiocyanatophenyl)diazenyl]-*N*,*N*-dimethylaniline	7612-98-8	53	0.7395	79	0.7442
1-Naphthylacetic anhydride	5415-58-7	54	0.7385	80	0.7426
4-Chloro-7-nitro-2,1,3-benzoxadiazole	10199-89-0	55	0.7376	34	0.8390
9*H*-Fluoren-9-ylmethyl carbonochloridate	28020-43-6	56	0.7358	81	0.7405
4-Methylbenzenesulfonyl chloride	98-59-9	57	0.7357	78	0.7462
2-Bromo-1-phenylethanone	70-11-1	58	0.7356	85	0.7390
1,1′,1″-(Chloromethanetriyl)tribenzene	76-83-5	59	0.7352	81	0.7405
1-Chlorocarbonylferrocene	1293-79-4			81	0.7405
4-Methoxybenzoyl chloride	100-07-2			81	0.7405
2-Bromo-1-(4-bromophenyl)ethanone	99-73-0	60	0.7351	85	0.7390
4-Methoxybenzenecarboximidamide	22265-37-8	61	0.7340	87	0.7371
1-(2-Pyridinyl)methanamine	3731-51-9	62	0.7338	87	0.7371
4-Nitrobenzoyl chloride	122-04-3	63	0.7333	90	0.7324
1*H*-Imidazol-1-yl(2-naphthyl)methanone	141903-34-6	64	0.7330	87	0.7371
3,5-Dinitrobenzoyl chloride	99-33-2	65	0.7294	90	0.7324
4-(Dimethylamino)benzoyl chloride	4755-50-4	66	0.7283	90	0.7324
9*H*-Fluoren-9-ylmethyl carbonochloridate	28920-43-6	67	0.7253	83	0.7405
1-(Bromomethyl)-4-nitrobenzene	100-11-8	68	0.7239	93	0.7296
4-{(*E*)-[4-(Dimethylamino)phenyl]diazenyl}benzenesulfonyl chloride	56512-49-3	69	0.7185	94	0.7232
2-Methoxy-5-(1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)benzenesulfonyl chloride	126565-42-2	70	0.7169	94	0.7232
4-Nitrophenyl carbonochloridate	7693-46-1	71	0.7168	97	0.7213
3-Methylbenzoyl chloride	1711-06-4	72	0.7154	98	0.7179
2-(4-Bromophenyl)-2-oxoethyl trifluoromethanesulfonate	93128-04-2	73	0.7104	99	0.7178
1-(Chloromethyl)-3,5-dinitrobenzene	74367-78-5	74	0.7104	101	0.7101
2-Bromo-1-(2-naphthyl)ethanone	613-54-7	75	0.7056	100	0.7164
(1*S*)-1-(9*H*-Fluoren-9-yl)ethyl carbonochloridate	107474-79-3	76	0.6977	102	0.7062
(2,4-Dinitrophenyl)hydrazine	119-26-6	77	0.6920	103	0.6926
2,4,6-Trinitrobenzenesulfonic acid	2508-19-2			104	0.6924
2,4-Dichloro-6-(4-ethoxy-1-naphthyl)-1,3,5-triazine	21614-17-5	78	0.6827	105	0.6825
N,4-Dimethyl-*N*-nitrosobenzenesulfonamide	80-11-5	79	0.6743	106	0.6818
1-Phenylmethanamine	100-46-9	80	0.6722	107	0.6793
4-Isocyanato-*N*,*N*-dimethylaniline	16315-59-6	81	0.6664	109	0.6653
6,7-Dimethoxy-4-methyl-3-oxo-3,4-dihydro-2-quinoxalinecarbonyl chloride	104077-15-8	82	0.6609	115	0.6591
4-Nitrobenzyl *N*,*N*′-diisopropylcarbamimidate	2978-11-2_	83	0.6587	118	0.6295
(3*Z*)-2-(Diphenylacetyl)-3-hydrazono-1-indanone	5102-79-4	84	0.6530	110	0.6647
1-Fluoro-2,4-dinitrobenzene	70-34-8				0.6641
9-Ethyl-9*H*-carbazol-3-amine	132-32-1	85	0.6526	112	0.6599
(4-Isothiocyanato-2,2,6,6-tetramethyl-1-piperidinyl)oxidanyl	36410-81-8			113	0.6592
(4-Nitrophenyl)hydrazine	100-16-3	86	0.6489	114	0.6592
4-(1-Pyrenyl)butanehydrazide	55486-13-0	87	0.6451	108	0.6663
4-Methylbenzenesulfonyl isocyanate	4083-64-1	88	0.6418	116	0.6499
Sodium hexafluorophosphate	21324-39-0			117	0.6349
4-Nitrobenzenediazonium tetrafluoroborate	456-27-9			119	0.6290
Benzenesulfonyl chloride	98-09-9	89	0.6208	120	0.6280
Isothiocyanatobenzene	103-72-0	90	0.6040	121	0.6067
2(1*H*)-Pyridinimine	504-29-0	91	0.5815	122	0.5874
1-Isocyanatonaphthalene	86-84-0	92	0.5577	123	0.5665

Table 5 *(Contd.)*

LC derivatisation agent	CAS number	High confidence rank	High confidence score	Low confidence rank	Low confidence score
9-(2-Carboxy-4-isothiocyanatophenyl)-6-(diethylamino)-*N*,*N*-diethyl-3*H*-xanthen-3-iminium chloride	36877-69-7			124	0.5561
Acetic anhydride	108-24-7	93	0.5136	125	0.5291
Isocyanatobenzene	103-71-9	94	0.5125	126	0.5255
1-Isothiocyanatonaphthalene	551-06-4	95	0.5036	127	0.5106
Benzoyl chloride	98-88-4	96	0.4962	129	0.4756
Phthalaldehyde	643-79-8	97	0.4861	128	0.4863
Hydroxylamine hydrochloride (1:1)	5470-11-01			130	0.4669
1,3-Dinitrobenzene	99-65-0	98	0.4041	131	0.4144
1,2-Benzenediamine	95-54-5	99	0.3994	132	0.4099
2-Sulfanylethanol	60-24-2	100	0.3644	133	0.3806

for this derivatisation agent are characterised by the best performance from the dataset. In contrast, a value equal to "0" means that all assessment criteria for a given derivatisation agent are characterised by the worst performance from the dataset. The values between "1" and "0" indicate how the alternative is similar or dissimilar to the ideal solution. For easier decision making, the signal word information of each derivatisation agent is included in Tables 5–7 and expressed with colours. "None" signal wording is highlighted in green, "warning" in amber and "danger" in red. In general terms, green coloured agents with "none" wording are ranked high and red "danger" agents are ranked low, as can be observed in Tables 5–7.

3.1. LC derivatisation agent assessment

The ranking of 133 LC derivatisation agents is presented in Table 5. According to the low confidence ranking, seven derivatisation agents, namely (3*R*,4*R*)-2,5-dioxotetrahydrofuran-3,4-diyldiacetate, 2,2′-dihydroxy-1*H*,1′*H*-2,2′-biindene-1,1′,3,3′(2*H*,2′*H*)-tetrone dihydrate, ferrocenecarboxaldehyde, 2-hydroxy-1,2-diphenylethanone, 2-acetylbenzaldehyde, and 9*H*-fluorene-2-carbaldehyde, are equally ranked as the 1st preference. The high confidence ranking includes only five out of these seven agents, and some differences between these agents are noticeable. Thus, 5,5-dimethyl-1,3-cyclohexanedione – the first rank according to low confidence ranking – is still within the first tertile but ranked 38th with high confidence ranking due to its relatively low boiling point and flash point, reduced removal during wastewater treatment and longer environmental residence time. 2-Hydroxy-1,2-diphenylethanone, a derivatisation agent also used as a food additive for human consumption,[28] remarkably ranked 2nd with high confidence ranking. 4-(Dimethylamino)benzaldehyde, a derivatisation agent of amino acids and peptides[22,29] known as Ehrlich' reagent, ranked 6th with high confidence ranking.

Remarkably, 8 out of 9 LC derivatisation agents included as restricted and priority substances in SUBSPORT,[30] SIN List,[31] and/or the EPA's Toxics Release Inventory (TRI) chemicals list[32] are ranked at the very bottom of the high confidence ranking (85–100). These chemicals included 9-ethyl-9*H*-carbazol-3-amine, benzenesulfonyl chloride, acetic anhydride, isocyanatobenzene, benzoyl chloride, hydroxylamine hydrochloride, 1,3-dinitrobenzene, and 1,2-benzenediamine, all of them labelled as dangerous compounds. (Bromomethyl) benzene is, on the other hand, an acylating agent identified with the signal word "warning" that has been ranked 24th by high confidence ranking. Even though this substance is not included in the SIN List and TRI chemicals list, it is not allowed in BSH products.[30]

The last agent in the ranking, 2-sulfanylethanol, is characterised by serious hazard and precautionary statements, including fatal effects. Characteristics of neighbouring agents are similar to 2-sulfanylethanol. Benzoyl chloride (rank 96 by the high confidence procedure) is even indicated by IARC as a probable human carcinogen. Benzoyl chloride is used for the derivatisation of hydroxyl-bearing compounds.[33,34] Phthalaldehyde (rank 97, according to high confidence ranking) is a derivatisation agent used for amine and thiol derivatisation[34,35] characterized by high toxicity towards rats (oral LD_{50} value equal to 178 mg kg^{-1}). Isocyanatobenzene (rank 94 with high confidence ranking), used for derivatisation of amines and hydroxyl-bearing compounds,[36–38] is not highly toxic towards rats (oral LD_{50} = 800 mg kg^{-1}), but is highly toxic towards rats through inhalation in a 4 h test (LC_{50} = 22 mg m^{-3}) and toxic towards *Danio rerio* in a 96 h test (LC_{50} = 84 mg L^{-1}).

3.2. GC derivatisation agent assessment

The assessment of GC derivatisation agents was performed with 98 compounds, and the obtained ranking is provided in Table 6. Most of the GC derivatisation agents considered in the study are used in alkylation/esterification (43%) and silylation (39%) reactions, whereas the remaining 18% are used as acylation agents. Five silylation agents, namely *N*-(trimethylsilyl)acetamide, trimethylsilyl (trimethylsilyl)carbamate, *N*-methyl-*N*-(trimethylsilyl)acetamide, 1-[dimethyl(2-methyl-2-propanyl)silyl]-1*H*-imidazole and *N*-[dimethyl(phenyl)silyl]-1,1-dimethyl-1-phenylsilanamine, four alkylation/esterification agents, namely butylboronic acid, 1,4,7,10,13,16-hexaoxacyclooctadecane, (diethoxymethoxy)ethane and 1,1-diethoxy-*N*,*N*-dimethylmethanamine, and one acylation agent, namely 2,2,6,6-tetramethyl-3,5-heptanedione, where ranked among the first 10 GC derivatisation agents in accordance with the high

Table 6 Assessment results of GC derivatisation agents

GC derivatisation agent	CAS number	High confidence rank	High confidence score	Low confidence rank	Low confidence score
Butylboronic acid	4426-47-5	1	0.8652	2	0.9829
2,2,6,6-Tetramethyl-3,5-heptanedione	1118-71-4	2	0.8611	1	1.0000
N-(Trimethylsilyl)acetamide	13435-12-6	3	0.8528	3	0.9344
Trimethylsilyl (trimethylsilyl)carbamate	35342-88-2	4	0.8452	3	0.9344
1,4,7,10,13,16-Hexaoxacyclooctadecane	17455-13-9	5	0.8299	6	0.8983
(Diethoxymethoxy)ethane	122-51-0	6	0.8260	5	0.9081
N-Methyl-*N*-(trimethylsilyl)acetamide	7449-74-3	7	0.8246	7	0.8962
1,1-Diethoxy-*N*,*N*-dimethylmethanamine	1188-33-6	8	0.8042	8	0.8740
2,3-Biphenyldiol	1133-63-7			9	0.8450
1-[(Aminooxy)methyl]-2,3,4,5,6-pentafluorobenzene hydrochloride (1:1)	57981-02-9			10	0.8435
1-[Dimethyl(2-methyl-2-propanyl)silyl]-1*H*-imidazole	54925-64-3	9	0.7684	11	0.8313
N-[Dimethyl(phenyl)silyl]-1,1-dimethyl-1-phenylsilanamine	3449-26-1	10	0.7647	11	0.8313
1-Methyl-*N*-[methyl(diphenyl)silyl]-1,1-diphenylsilanamine	7453-26-1	11	0.7638	11	0.8313
N,*N*,*N*-Tributyl-1-butanaminium tetrabutylborate(1-)	23231-91-6			14	0.8248
1,1,1,2,2,3,3,4,4-Nonafluoro-4-iodobutane	423-39-2	12	0.7579	15	0.8212
(Aminooxy)ethane hydrochloride (1:1)	3332-29-4			16	0.8174
1,3-Bis(trimethylsilyl)urea	18297-63-7			17	0.8042
(Pentafluorophenyl)hydrazine	828-73-9	13	0.7379	19	0.7962
(3*E*)-4-[(Trimethylsilyl)oxy]-3-penten-2-one	13257-81-3	14	0.7245	18	0.7970
2,2,3,3,4,4,4-Heptafluoro-*N*-(2,2,3,3,4,4,4-heptafluorobutanoyl)-*N*-methylbutanamide	73980-71-9			19	0.7962
Dimethylsilanediyl diacetate	2182-66-3	15	0.7220	27	0.7665
Chloro(triisopropyl)silane	13154-24-0	16	0.7213	29	0.7636
1,1-Bis(2,2-dimethylpropoxy)-*N*,*N*-dimethylmethanamine	4909-78-8	17	0.7181	21	0.7859
2-Bromo-1-phenylethanone	70-11-1	18	0.7176	31	0.7611
N,*N*-Dimethyl-1,1-dipropoxymethanamine	6006-65-1	19	0.7172	21	0.7859
N,1,1,1-Tetramethyl-*N*-(trimethylsilyl)silanamine	920-68-3	20	0.7165	21	0.7859
N,*N*-Dimethyl-1,1-bis[(2-methyl-2-propanyl)oxy]methanamine	36805-97-7	21	0.7159	21	0.7859
Chloro(2-methyl-2-propanyl)diphenylsilane	58479-61-1	22	0.7151	29	0.7636
2,2,3,3,3-Pentafluoro-1-propanol	422-05-9	23	0.7139	25	0.7835
Pentafluorobenzaldehyde	653-37-2			25	0.7835
Trimethylsilyl 2-methyl-2-propene-1-sulfinate	723336-86-5			31	0.7611
Triethylsilyl 2-methyl-2-propene-1-sulfinate	850418-19-8			31	0.7611
Dimethyl(2-methyl-2-propanyl)silyl 2-methyl-2-propene-1-sulfinate	850418-20-1			31	0.7611
Pentafluoropropionic anhydride	356-42-3	24	0.7130	40	0.7561
Heptafluorobutanoic anhydride	336-59-4	25	0.7129	40	0.7561
Dimethyl(2-methyl-2-propanyl)silyl(1*E*)-*N*-[dimethyl(2-methyl-2-propanyl)silyl]ethanimidate	82112-21-8	26	0.7099	39	0.7579
Heptafluorobutanoic acid	375-22-4	27	0.7087	40	0.7561
Trimethyloxonium tetrafluoroborate	420-37-1			43	0.7521
2,2-Dimethoxypropane	77-76-9			44	0.7507
1-(Bromomethyl)-4-nitrobenzene	100-11-8	28	0.7058	47	0.7450
Chloro(dimethyl)(pentafluorophenyl)silane	20082-71-7	29	0.7052	45	0.7498
Pentafluorobenzoyl chloride	2251-50-5	30	0.7046	46	0.7475
1-(Bromomethyl)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene	76437-40-6	31	0.7031	49	0.7424
1-(Bromomethyl)-2,3,4,5,6-pentafluorobenzene	1765-40-8	32	0.7013	49	0.7424
2,2,2-Trifluoro-1-(1*H*-imidazol-1-yl)ethanone	1546-79-8	33	0.7000	35	0.7582
Ethyl trifluoromethanesulfonate	425-75-2	34	0.6997	49	0.7424
Triisopropylsilyl trifluoromethanesulfonate	80522-42-5	35	0.6981	49	0.7424
N-[Dimethyl(2-methyl-2-propanyl)silyl]-2,2,2-trifluoro-*N*-methylacetamide	77377-52-7	36	0.6971	35	0.7582
Chloro(dimethyl)(2-methyl-2-propanyl)silane	18162-48-6	37	0.6962	48	0.7431
2,2,3,3,4,4,4-Heptafluoro-*N*-methyl-*N*-(trimethylsilyl)butanamide	53296-64-3	38	0.6927	35	0.7582
2,2-Dimethylpropanoic anhydride	1538-75-6	39	0.6906	53	0.7415
Dimethyl(2-methyl-2-propanyl)silyl (1*E*)-*N*-[dimethyl(2-methyl-2-propanyl)silyl]-2,2,2-trifluoroethanimidate	87020-42-6			55	0.7370
4-Bromobenzyl bromide	589-15-1	40	0.6896	56	0.7363
Bromo(trimethyl)silane	2857-97-8	41	0.6871	57	0.7360
Triethyloxonium hexafluorophosphate	17950-40-2			58	0.7321
Trifluoroacetic anhydride	407-25-0			59	0.7313
1,1,1,2,2-Pentafluoro-2-iodoethane	354-64-3	42	0.6842	28	0.7638
2,2,2-Trichloroethanol	115-20-8	43	0.6777	60	0.7306
2-Thiophenecarbaldehyde	98-03-3	44	0.6754	54	0.7395
2,2,3,3,3-Pentafluoro-1-(1*H*-imidazol-1-yl)-1-propanone	71735-32-5	45	0.6726	62	0.7184
Methyl trifluoromethanesulfonate	333-27-7	46	0.6701	62	0.7184
2,2,2-Trifluoro-*N*-methyl-*N*-(trimethylsilyl)acetamide	24589-78-4	47	0.6694	35	0.7582
2,2,2-Trifluoro-*N*-methyl-*N*-(trifluoroacetyl)acetamide	685-27-8	48	0.6664	67	0.7133

Table 6 *(Contd.)*

GC derivatisation agent	CAS number	High confidence rank	High confidence score	Low confidence rank	Low confidence score
2,2,2-Trifluoro-*N*,*N*-bis(trimethylsilyl)acetamide	25561-30-2	49	0.6657	67	0.7133
Trimethylboroxine	823-96-1	50	0.6638	61	0.7217
N,*N*,*N*′,*N*′,1,1-Hexamethylsilanediamine	3768-58-9	51	0.6585	64	0.7145
N,*N*-Diethyl-1,1,1-trimethylsilanamine	996-50-9	52	0.6584	64	0.7145
Sodium methanolate	124-41-4			68	0.7069
N-(Dimethylsilyl)-1,1-dimethylsilanamine	15933-59-2			69	0.7058
Propanoic anhydride	123-62-6	53	0.6574	71	0.7035
N,*N*,1,1,1-Pentamethylsilanamine	2083-91-2	54	0.6496	72	0.7030
1-(Trimethylsilyl)-1*H*-imidazole	18156-74-6	55	0.6465	70	0.7058
Dimethyl(2-methyl-2-propanyl)silyl trifluoromethanesulfonate	69739-34-0	56	0.6431	74	0.6968
Trimethylsilyl (1*E*)-*N*-(trimethylsilyl)ethanimidate	10416-59-8	57	0.6424	73	0.7004
Hexamethyldisiloxane	107-46-0	58	0.6355	75	0.6960
Chloroacetic anhydride	541-88-8			76	0.6801
Chloro(triethyl)silane	994-30-9	59	0.5984	77	0.6596
2-Bromopropane	75-26-3	60	0.5867	78	0.6508
Isobutyl carbonochloridate	543-27-1	61	0.5789	79	0.6430
Hexyl carbonochloridate	6092-54-2	62	0.5533	80	0.6198
Trichloroacetyl chloride	76-02-8	63	0.5513	81	0.6188
Chloro(trimethyl)silane	75-77-4	64	0.5356	82	0.6062
Thionyl dichloride	7719-09-7			83	0.5984
1,1,1,3,3,3-Hexafluoro-2-propanol	920-66-1	65	0.5280	86	0.5835
1,1-Dimethoxy-*N*,*N*-dimethylmethanamine	4637-24-5	66	0.5166	85	0.5877
1-(Trimethylsilyl)-1*H*-imidazole-pyridine (1:1)	8077-35-8			87	0.5809
Chloro(dimethyl)silane	1066-35-9	67	0.5129	84	0.5903
Acetic anhydride	108-24-7	68	0.4927	88	0.5654
1,1,1-Trimethyl-*N*-(trimethylsilyl)silanamine	999-97-3	69	0.4640	90	0.5391
Trichloroborane	10294-34-5	70	0.4614	89	0.5469
Trifluoroborane	7637-07-2			91	0.5363
2,2,2-Trifluoroethanol	75-89-8			92	0.5171
N,*N*,*N*-Trimethylanilinium hydroxide	1899-02-1			93	0.4540
Trimethylsulfonium hydroxide	17287-03-5			94	0.4506
Sulphuric acid solution	7664-93-9			95	0.4307
Methanol, hydrochloride (1:1)	132228-87-6			96	0.3899
N,*N*,*N*-Trimethylmethanaminium hydroxide	75-59-2			97	0.3521
Dimethyl sulphate	77-78-1	71	0.1732	98	0.1857

confidence ranking. The highest rank of fluorinated compounds (1-[(aminooxy)methyl]-2,3,4,5,6-pentafluorobenzene hydrochloride) is 10 according to the low confidence ranking.

The least preferable derivatisation agent according to both rankings is dimethyl sulphate, a chemical used in alkylation and esterification reactions that is characterised by many hazard and precautionary statements and categorised by IARC as a probable human carcinogen. This compound is characterised by high toxicity in rats with an LC_{50} = 45 mg m^{-3} in a 4 hour-exposure test and towards *Lepomis macrochirus* with an LC_{50} = 7.5 mg L^{-1} in a 96 h test, as stated in MSDS. Also commonly applied derivatisation agents, such as a methanol and hydrochloric acid mixture or sulphuric acid are ranked very low, although they are assessed with the low confidence ranking only.

Acetic anhydride (rank 68 according to the high confidence ranking) is a commonly applied acylating agent in GC determinations. It is well characterised in terms of its toxicological parameters, oral toxicity towards rats (LD_{50} = 630 mg kg^{-1}), inhalation toxicity towards rats in a 6 h test (LC_{100} = 400 ppm), dermal toxicity towards rabbits (LD_{50} = 4320 mg kg^{-1}), and towards aquatic organisms like *Leuciscus idus melanotus* in a 48 h test (LC_{50} – 265 mg L^{-1}), *Daphnia* in a 96 h test (EC_{50} = 55 mg L^{-1}) and *Desmodesmus subspicatus* in a 192 h test (EC_{10} = 3400 mg L^{-1}). Among other applications, acetic anhydride has been used for the *in situ* conversion of phenols into their corresponding acetyl derivatives.[39] Similarly, trifluoroacetic anhydride (rank 59 according to the low confidence ranking) has been applied to obtain derivatives of amphetamine-type stimulants for their determination in biological samples.[40] Pentafluorobenzaldehyde (rank 25 according to the low confidence ranking) has been applied to obtain aliphatic amine derivatives directly on solid phase microextraction (SPME) fibers.[41] *N*-Methyl-*N*-(trimethylsilyl)acetamide (high rank 7 according to both rankings) has been applied for the derivatisation of nitrophenols in hollow fibre liquid phase microextraction prior to their determination in environmental samples.[42] Even though a rather green derivatisation agent is applied in a small amount (25 μL of 10 mg L^{-1}), the main emphasis in terms of green chemistry is on the small amounts of solvent applied in the procedure. A mixture of three trimethylsilylating agents, namely 1-(trimethylsilyl)-1*H*-imidazole (rank 53 according to the high confidence ranking), trimethylsilyl (1*E*)-*N*-(trimethylsilyl)ethanimidate (rank 57 according to

Table 7 Assessment results of chiral derivatization agents

Chiral derivatisation agent	CAS number	High confidence rank	Low confidence score	Low confidence rank	Low confidence score
(*S*)-6-Methoxy-2,5,7,8-tetramethyl-2-chromanecarboxylic acid	135806-59-6	1	0.9100	1	1.0000
(*R*)-6-Methoxy-2,5,7,8-tetramethyl-2-chromanecarboxylic acid	139658-04-1	1	0.9100	1	1.0000
(2*S*,3*S*)-2,3-Butanediol	19132-06-0	3	0.8887	1	1.0000
(3a*S*)-3a-Allyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan	1052236-86-8			1	1.0000
(1*S*,2*R*,4*S*,6*R*,7*S*,1′*S*,2′*R*,4′*S*,6′*R*,7′*S*)-4,4′-Oxybis(1,10,10-trimethyl-3-oxatricyclo[5.2.1.02,6]decane)	108031-79-4	4	0.8437	1	1.0000
N-Isobutyryl-L-cysteine	124529-02-8	5	0.7720	6	0.7898
N-Isobutyryl-D-cysteine	124529-07-3	5	0.7720	6	0.7898
(1-Isothiocyanatoethyl)benzene	24277-43-8	7	0.7692	6	0.7898
2,3,4,6-Tetrakis-*O*-(2,2-dimethylpropanoyl)-*N*-(thioxomethylene)-β-D-glucopyranosylamine	958300-06-6			6	0.7898
(2*R*)-2-Octanol	5978-70-1	8	0.6523	10	0.6611
(1*R*)-1-(1-Naphthyl)ethanamine	3886-70-2	9	0.6188	11	0.6228
3,3,3-Trifluoro-2-methoxy-2-phenylpropanoic acid	17257-71-5	10	0.6153	12	0.6163
(2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoic acid	81655-41-6	10	0.6153	12	0.6163
(2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoic acid	20445-31-2	12	0.6142	12	0.6163
4,12-Dimethyl-1,9-diazatetracyclo[7.7.1.02,7.010,15]heptadeca-2,4,6,10,12,14-hexaene	14645-24-0	13	0.6126	12	0.6163
5,13-Dimethyl-1,9-diazatetracyclo[7.7.1.02,7.010,15]heptadeca-2,4,6,10,12,14-hexaene	21451-74-1	14	0.6124	12	0.6163
2,3,4,6-Tetrakis-*O*-(2,2-dimethylpropanoyl)-*N*-(thioxomethylene)-β-D-galactopyranosylamine	147948-52-5			17	0.5820
(1*S*)-1-(Pentafluorophenyl)ethanol	104371-20-2	15	0.5731	17	0.5820
(2*S*)-2-Hydroxybutanoic acid	3347-90-8	16	0.5618	21	0.5508
*N*2-(5-Fluoro-2,4-dinitrophenyl)-L-valinamide	132679-61-9	17	0.5601	19	0.5615
*N*2-(5-Fluoro-2,4-dinitrophenyl)-D-valinamide	210529-62-7	17	0.5601	19	0.5615
4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl chloride	39637-74-6	19	0.5559	22	0.5480
(1*R*,4*S*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl chloride	104530-16-7	20	0.5543	22	0.5480
[(1*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methanesulfonyl chloride	39262-22-1	21	0.5230	24	0.5202
(1*R*)-1-Phenylethanol	1517-69-7	22	0.4908	25	0.4747
(1*S*)-1-Phenylethanol	1445-91-6	23	0.4907	25	0.4747
(1*S*)-1-(9*H*-Fluoren-9-yl)ethyl carbonochloridate	107474-79-3	24	0.4508	27	0.4380
(1*R*,2*S*,5*S*)-2-Isopropyl-5-methylcyclohexyl carbonochloridate	14602-86-9	25	0.4350	28	0.4121
(1*R*)-1-Phenylethanamine	3886-69-9	26	0.3741	29	0.3581
(1*S*)-1-Phenylethanamine	2627-86-3	27	0.3465	30	0.3267
2,3,4-Tri-*O*-acetyl-*N*-(thioxomethylene)-α-D-arabinopyranosylamine	62414-75-9			31	0.2882
2,3,4,6-Tetra-*O*-acetyl-*N*-(thioxomethylene)-β-D-glucopyranosylamine	14152-97-7	28	0.3290	31	0.2882
(1-Isothiocyanatoethyl)benzene	24277-44-9	29	0.3194	31	0.2882
1-[(1*R*)-1-Isocyanatoethyl]naphthalene	42340-98-7	30	0.2280	34	0.1767
[(1*S*)-1-Isocyanatoethyl]benzene	14649-03-7	31	0.1919	35	0.1324
[(1*R*)-1-Isocyanatoethyl]benzene	33375-06-3	32	0.1795	36	0.1161

the high confidence ranking), and chloro(trimethyl)silane (rank 64 according to the high confidence ranking), has been applied for the derivatisation of polycyclic aromatic hydrocarbon quinines.[43] The overall greenness of the analytical procedure was assessed with the analytical eco-scale giving positive results. Our assessment shows that these three derivatisation agents are rather problematic among those used in GC.

In another work, 1-(bromomethyl)-2,3,4,5,6-pentafluorobenzene (rank 32 according to the high confidence ranking), 1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine (rank 69 according to the high confidence ranking), 2,2,2-trifluoro-*N*,*N*-bis(trimethylsilyl)acetamide (rank 49 according to the high confidence ranking), *N*-[dimethyl(2-methyl-2-propanyl)silyl]-2,2,2-trifluoro-*N*-methylacetamide (rank 36 according to the high confidence ranking), and acetic anhydride (rank 68 according to the high confidence ranking) were investigated in terms of applicability as SPME on-fibre derivatisation agents for phenol determination in occupational air.[44] The best analytical performance was achieved with acetic anhydride, an agent that was ranked low in this assessment. The agent of the best rank here, 1-(bromomethyl)-2,3,4,5,6-pentafluorobenzene (rank 32 according to the high confidence ranking), was characterised by good analytical performance in the discussed study.

A number of GC derivatisation agents have been identified as restricted and priority substances in SUBSPORT, the SIN List, and/or the EPA's TRI chemicals list. Specifically, two silylating reagents, namely hexamethyl disiloxane and chloro(trimethyl)silane, three acylating agents, namely heptafluorobutanoic acid, propanoic anhydride and acetic anhydride, and eight alkylation/esterification agents, namely sodium methanoate, propanoic anhydride, 2-bromopropane, trichloroacetyl chloride, trichloroborane, trifluoroborane, sulphuric acid solution and dimethyl sulphate have been ranked, in general, within the third tertile of both high and low confi-

dence rankings with the exception of heptafluorobutanoic acid, a fluorinated substance restricted in textile production.[30]

3.3. Chiral derivatisation agents assessment

It can be inferred from the basic statistics analysis of transformed hazard and precautionary statements, signal wordings and degradation products that chiral derivatisation agents are, in general, less problematic than LC and GC derivatisation agents. The mean value of hazard statements for chiral derivatisation agents is 8.7 (LC = 10.3 and GC = 13.6), precautionary statements is 20.6 (LC = 21 and GC = 31.9), signal wording is 2.08 (LC = 2.02 and GC = 3.04) and degradation/fire products is 17.3 (LC = 19.3 and GC = 18.0). None of the chiral agents is listed as a carcinogen in the IARC lists. It should be noted, however, that the assessment criteria applied here do not include all parameters that are dependent on the chirality, *i.e.*, toxicity towards different organisms or teratogenicity,[45] and, therefore, they have not been included during ranking procedures as these compounds are still weakly characterised.

Among chiral derivatisation agents, the (*R*)- and (*S*)-forms of 6-methoxy-2,5,7,8-tetramethyl-2-chromanecarboxylic acid, (2*S*,3*S*)-2,3-butanediol, (1*S*,2*R*,4*S*,6*R*,7*S*,1′*S*,2′*R*,4′*S*,6′*R*,7′*S*)-4,4′-oxybis(1,10,10-trimethyl-3-oxatricyclo[5.2.1.02,6]decane), and (3a*S*)-3a-allyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan obtained the highest scores with both high and low confidence. The most problematic chiral derivatisation agents were found to be benzene and naphthalene derivatives. But even these compounds are not labelled with "fatal" effects hazard statements. (1*S*)-1-Phenylethanamine (rank 27 according to the high confidence ranking) is rather well characterized in terms of toxicity – oral toxicity for rats (LD_{50} = 950 mg kg^{-1}), and dermal toxicity towards rabbits (LD_{50} = 730 mg kg^{-1}) and to *Pimephales promelas* fish in a 96 h test (LC_{50} = 17 mg L^{-1}). In general, isocyanate and isothiocyanate reagents were ranked low. In fact, five of them have received the lowest scores, namely 2,3,4,6-tetra-*O*-acetyl-*N*-(thioxomethylene)-β-D-glucopyranosylamine, (1-isothiocyanatoethyl)benzene, 1-[(1*R*)-1-isocyanatoethyl] naphthalene, [(1*S*)-1-isocyanatoethyl]benzene and [(1*R*)-1-isocyanatoethyl]benzene. None of the chiral derivatisation agents have been identified as restricted and priority substances in SUBSPORT, the SIN List, and/or the EPA's TRI chemicals list.

4. Conclusions

The present study provides an assessment, in terms of greenness, of 267 LC, GC and chiral derivatisation agents typically used in analytical chemistry and related fields. The preference rankings were performed for each group of derivatisation agents by means of MCDA according to the best relevant criteria that are available. In all three cases, fine rankings were obtained for high and low confidence assumptions.

For more informative assessment, it would be beneficial to include toxicological endpoints and more information about environmental persistence among the assessment criteria. Incorporating valuable greenness indicators of synthesis processes such as the carbon footprint or energy needs during the production of each chemical as assessment criteria would be worthwhile. Unfortunately, these values are not easily available in the literature for a satisfactory number of derivatisation agents. Furthermore, the recovery of derivatisation agents is another important issue that influences the greenness of derivatisation reactions, so its inclusion as an assessment criterion would also be desirable. However, it is dependent on reaction specific conditions, not only the kind of derivatisation agent matters, but also the analytes to be determined and solvents employed.

The greenness of derivatisation agents is very rarely considered during analytical method development. The main criteria for the selection of derivatisation agents are their rapidity and efficiency, but the greenness should also be considered. This study allows selecting less problematic derivatisation agents for analytical method development while some clues can also be deduced for other than analytical applications.

Conflicts of interest

There are no conflicts to declare.

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