

Article

Green Chemistry's Contribution to the Kamal Qureshi Protocol: Comparing Various Activating Modes, the Use of Bentonitic Clay as the Catalyst, and the Use of a Green Solvent

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Abstract: After attending both the “Decade to Educate in the Sustainable Development and the Agenda 30 of the UNESCO” and the “ACS GCI Pharmaceutical Roundtable”, which focused on sustainable chemistry, in this article, a green chemistry contribution to the Kamal Qureshi protocol is offered; thus, DIM[®] and several of its analogs (3,3'-diindolylmethanes) were suitably produced under the green chemistry protocol. In the first stage, the substrate indol-3-yl carbinol was evaluated using mechanochemistry (the best mode) in comparison to other activating methods (near-infrared and microwave electromagnetic irradiation and ultrasound), wishing to highlight the employment of both TAFF[®], an excellent and well-characterized natural catalyst (bentonitic clay), and acetone, a green solvent, in addition to the analysis of the procedures in real-time. In the second stage, the mechanochemical methodology was extended to produce a set of fifteen DIMs, in the last stage, the use of a green metric exhibited the greenness of the approach, with it being important to highlight that, to our knowledge, after a search in the literature, this is the first time that the process has been evaluated to demonstrate its greenness.

Keywords: DIM[®]; diindolylmethanes; green chemistry; mechanochemistry; mechanochemical activation; microwave–infrared ultrasound; bentonitic clay catalyst

1. Introduction

Chemistry is unfortunately known for its negative environmental impact; consequently, chemists have been concerned with controlling damage to the ecosystem through the protocol of Green Chemistry (GCh), known as the “12 Principles of Green Chemistry” [1]. The use of this template is an excellent way to solve problems caused by pollutants. The GCh protocol implies a paradigm involving the use of preventive chemistry to eliminate or at least minimize the generation of pollutants. It is also worth noting that green chemistry efforts aim to achieve reactions that contemplate eco-conditions, bearing in mind the vision of an ideal synthesis [2–4]. Related to the GCh protocol, it must

be highlighted that UNESCO, some years ago, established the “Decade of Education for Sustainable Development (DESD), 2005–2014”, comprising the conception of education as teaching—researching—informing [5]; in this sense, chemists have a route to contribute to sustainable development (SD).

According to the GCh protocol, Principle #6 “Energy efficiency” considers several forms in which to activate a reaction, among the most common, are near-infrared irradiation (NIR) [6,7], microwave irradiation (MW) [8], ultrasound (US) [9], and, of particular interest for this work, mechanochemistry (MCh), also known as tribochemistry (TCh) [10]. It is convenient to consider that TCh or MCh proceeds through friction and collisions between the materials; MCh (also called grinding) is handily carried out in a mortar with a pestle, while TCh involves the use of mechanical devices. To highlight the undeniable actuality of the tribochemical process, the high-speed ball milling procedure (TCh-HSBM) is used as an example, performed in a planetary mill [11,12]. Related to Principle #9 “Catalysis”, considered a fundamental pillar of GCh [13], Tonsil Actisil FF[®] (TAFF[®]), a bentonitic clay, has been employed as an excellent green catalyst or support [14]; in this sense [vide supra], it is convenient to highlight that a detailed study to characterize TAFF[®] has been previously performed, exhibiting, in consequence, its excellent catalytic properties through the use of ²⁹Si and ²⁷Al MAS-NMR, X-ray diffraction, X-ray fluorescence, scanning electron microscopy, IR spectrophotometry, thermal analysis (DTA, TG-DTG), and adsorption techniques (N₂-BET). In this sense, the X-ray powder diffractogram showed the presence of a phase with *d* values of 13.7, 4.47, and 3.21, corresponding to the patterns of a montmorillonitic mineral (Na_{0.3}(Al, Mg)₂Si₄O₁₀(OH)₂·X H₂O), the catalytic support of the clay. In addition, a BET surface area of 198.7 m² g^{−1}, and a pore volume and diameter average of 32.04 × 10^{−2} cm³ g^{−1} and 77.8 Å, respectively, imply the presence of a very good catalyst; moreover, the acidic nature of the surface (catalytic) of clay was determined by IR spectrophotometry, employing pyridine as a reagent indicator molecule; it exhibited both a pyridinium ion (1543.6 cm^{−1}, Brönsted–Lowry site) and coordinated pyridine (1448 cm^{−1}, Lewis site).

On the other hand, diindolylmethane (DIM[®]), or 3,3′-diindolylmethane, is originally produced from a natural artifact intermediate, indole-3-carbinol (I3C), as a consequence of the pH in the stomach; it is convenient to note that I3C is found in the form of thiohydroximate-*O*-sulfonate (a natural indole glucosinolate) in many cruciferous vegetables (broccoli, Brussels sprouts, cabbage, and kale) and that the dietary consumption of this class of vegetables shows positive effects on several health-related fields; this is in addition to the fact that DIM[®] has shown cancer preventative effects [15–21], suppressing tumor growth and overcoming tumor resistance through the induction of tumor suppressor miRNAs of oncomirs [22].

Also, it is worth noting that the indolyl moiety appears in a broad range of pharmacologically and biologically active compounds [23]; moreover, many DIM derivatives (DIMs) are found in bioactive metabolites of terrestrial and marine origin [24–27]; consequently, there is great interest in the production of this kind of molecules.

Related to DIMs, the Kamal Qureshi protocol [28] is the typical procedure used for their production, involving a mixture of two equivalents of indole and one equivalent of an aldehyde, in the presence of an acid catalyst. In this sense, it is convenient to mention that this process involves a multicomponent reaction (MCR); in particular [KQ-3MCR], the MCR is a process that involves the mixture of three or more reagents (components) to produce a unique product, with a higher atom economy (GCh Principle #2), without workup, generally requiring only the isolation of the final product [29]. At present, several procedures have been developed to improve the conditions and yield such as the condensation between indole and several alcohols using a ruthenium catalyst, at 140 °C [30]. Another

interesting example was recently reported [31] employing the Friedel-Crafts reaction using water as a solvent and *N*-heterocyclic iod(az)olium salt as a catalyst. Nallagangula et al. reported in 2003 [32], the production of diindolylmethanes by interrupted borrowing hydrogen strategy, employing an iridium catalyst. Also, a green strategy was reported by Pasuparthi and Maiti in 2024 [33], avoiding the use of metal synthesis but using an ionic liquid [BCMIM][Cl] at room temperature. However, these experimental conditions are, in general, hard, non-environmentally friendly, and involve expensive catalysts.

Of particular interest for this search, and according to Principle #6 of GCh, it is important to highlight the mechanochemical practice of using a mortar/pestle, at room temperature to activate this kind of reaction; in this sense, after a deep literature search and consequently to our knowledge, the published processes involve mainly non-friendly and expensive catalysts (Table 1).

Table 1. General processes to produce DIMs, by mechanochemistry.

Product Reported ¹	General Reaction Condition	Average Yield (%)	Reference
3–5, 6, 10–12	Indole, aromatic aldehyde, cat. ² prolinium hydrogen sulfate, solvent-free, support-free, hand-grinding at rt ³ , 5 min.	88	[34]
3–6, 12	Indole, aromatic aldehyde, cat. ² HCl-SiO ₂ , mortar/pestle, rt ³ , 20 min.	88	[35]
3–4, 12	Indole, aromatic aldehyde, cat. ² Sc(OTf) ₃ , solvent, ground at rt ³ , 110 min.	60	[36]
3–6, 10, 12	Indole, aromatic aldehyde, cat. ² silica gel, ball milling using 10 balls, 20 min.	82	[37]
3, 6, 10–11	Indole, aromatic aldehyde, cat. ² Bi(OTf) ₃ , grinding, rt ³ , 8 min.	79	[38]
3–6, 12	Indole, aromatic aldehyde, cat. ² BiCl ₃ -MK10, mortar/pestle, rt ³ , 4 min.	85	[39]
3, 6, 11–12	Aromatic aldehyde or substituted hydrazone, indole, cat. ² Fe ³⁺ -montmorillonite K10, mortar/pestle, 4 min.	91	[40]
3–6, 12	Indole, aromatic aldehyde, cat. ² TiO ₂ -SO ₄ ^{2−} , ground mortar/pestle at rt ³ .	79	[41]
3–5, 11–12	Aromatic aldehyde, indole, cat. ² silica gel, mortar/pestle, 20 min.	55	[42]
-	Indole, aromatic aldehydes, cat. ² XSA, grinding.	87	[43]
3–4, 6, 9, 12	Indole, aromatic aldehyde, cat. ² <i>N</i> -sulfonic acid poly(4-vinylpyridinium), pestle/mortar at rt ³ , solvent-free.	82	[44]
3–4, 6, 11	Indole, aromatic aldehyde, cat. ² phosphate-impregnated titania, solvent-free, mortar/pestle at rt ³ , 1 min.	72	[45]
3–6, 10–11	Poly(4-vinylpyridinium)hydrogen sulfate, indole, and aryl aldehyde, mortar/pestle at rt ³ , 14 min.	91	[46]
3–6, 8, 11–12	Indole, aromatic aldehyde or ketone, cat. ² SiO ₂ -AlCl ₃ , mortar/pestle at rt ³ , 40 min.	78	[47]
3–6, 10–12	Aldehyde or ketone, indole, cat. ² silicotungstic acid, mortar/pestle at rt ³ .	70	[48]
3–6, 9, 11–12	Indole, aldehyde or ketone, cat. ² TCCA, mortar/pestle, 5 min.	87	[49]
3–4, 6, 11–12	Indole, aromatic aldehyde, cat. ² bismuth nitrate, mortar/pestle at rt ³ , 11 min.	89	[50]
3–6, 11–12	Indole, aromatic aldehyde, cat. ² SbCl ₃ , mortar/pestle at rt ³ , 15 min.	81	[51]
3–4, 6, 12	Indole, aromatic aldehyde, cat. ² CSA, mortar/pestle at rt ³ .	89	[52]
3, 5–6, 8, 11–12	Indole, aromatic aldehyde, cat. ² Bi(NO ₃) ₃ •5H ₂ O, pestle/mortar, 7 min.	81	[53]
2–3	Indole, aldehyde, cat. ² HBF ₄ -SiO ₂ , mortar/pestle, 10 min.	86	[54]
3–4, 6, 9	Aromatic aldehyde, indole, cat. ² sulfamic acid, mortar/pestle, 25 °C, 5 min.	81	[55]
3–4, 6, 12	Indole, aromatic aldehyde, cat. ² <i>p</i> -TSA, mortar/pestle at 25 °C.	78	[56]
3–6, 12	Aromatic aldehyde, indole, I ₂ , mortar/pestle at rt ³ , 10 min.	82	[57]

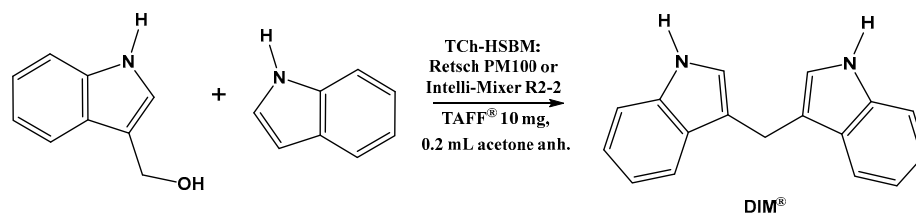
¹ The numbers correspond to products previously reported and obtained in this work. ² Catalyst. ³ Room temperature.

As a part of our research program, attending the emergent request of UNESCO to contribute to the DESD, we are conveniently involved in the GCh-protocol producing many classes of heterocyclic compounds with diverse important pharmacological uses [58–67], wishing to highlight the practice of green metrics to accomplish appropriated greener analysis [68]. Therefore, the goal of this paper is to offer a green approach to produce DIM[®] from IC3, and a set of DIMs by MCR between indole and several aldehydes, in addition to contributing to the Kamal Qureshi, reaction mechanism, validating the presence of its product-intermediate (I3C): comparing MCh/TCh-HSBM, US, NIR, and MW as activating reaction modes, employing TAff[®] a bentonitic clay as a green catalyst, in the presence of acetone as green solvent, using GC-MS to perform analysis in real time for an appropriate reaction monitoring.

2. Results and Discussion

2.1. Mechanochemical Production of DIM[®]

As can be seen in Table 1, the mortar/pestle procedure is a typical method to produce DIMs, thus, it was the first strategy to evaluate, at 25 °C under solventless conditions, using TAFF[®] as the catalyst; however, it is important to highlight that under this strategy the hand use-conditions are irregular to keep a suitable control. Consequently, it was considered convenient to evaluate “two tribochemical techniques” (HSBM–Retsch PM100 and mixer Intelli-Mixer R2-2 devices). Accordingly, the summarized conditions and results are exhibited in Scheme 1 and Table 2, and as complement Figures S1 and S2.



Scheme 1. Mechanochemical production of DIM.

Table 2. Production of DIM[®] ¹.

(a)		TCh-HSBM Device: PM100. Time Reaction: 30 min			
Frequency (rpm)/% formation from GC-MS		100/0.00	200/0.97	300/6.30	400/18.35
(b)		TCh-HSBM device: PM100. Time reaction: 60 min			
Frequency (rpm)/% formation from GC-MS		100/25.1	200/57.8	300/73.6	400/78.5
(c)		Intelli-Mixer R2-2. Time reaction: 15 min			
Frequency (rpm)/% formation from GC-MS		25/59.6	50/66.9	75/77.6	99/80.1

¹ See materials and methods section.

According to Table 2a,b, the best reaction conditions are those corresponding to 60 min at 400 rpm (78.5% of formation) for the PM100 device, and 15 min at 99 rpm (80.1% of formation) for the Intelli-Mixer R2-2 (Table 2c).

Regarding the catalytic action of the TAFF[®], it must be provoked by the enhancement of the electrophilic character of the methylene carbon linked to the hydroxyl group in I3C, due to the fact of dual acidic features, Lewis (L) and Brönsted-Lowry (BL), created by Al³⁺ (substituted by Mg²⁺), and the Si-OH group, respectively. [14], Figure 1.

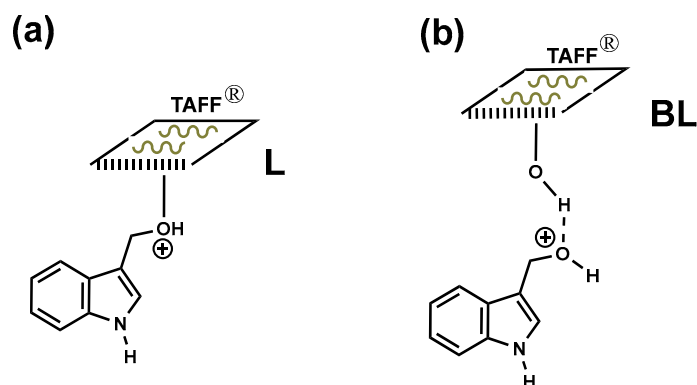


Figure 1. Electrophilic character promoted by the acid sites of TAFF[®] interacting with the hydroxyl group of the I3C; Lewis (a), and by Brönsted-Lowry (b).

2.2. DIM[®] Production Comparing Diverse Activating Procedures

It is important to note that the production of DIM[®] was also evaluated by comparing other activation modes, NIR, MW, and US; the corresponding results are summarized in Table 3. In addition, suitable comparative percentages of formation are displayed in Figure 2, and in complement the respective analysis in real-time by GC-MS can be consulted in Figures S3–S5.

Table 3. DIM[®] production employs different activating methods.

Alternative Activation Source ¹	Experiment	% Formation by GC-MS
NIR	1	63.75
	2	65.41
	3	65.10
MW	1	25.19
	2	24.98
	3	26.20
US	1	42.36
	2	41.09
	3	41.27

¹ See materials and methods section.

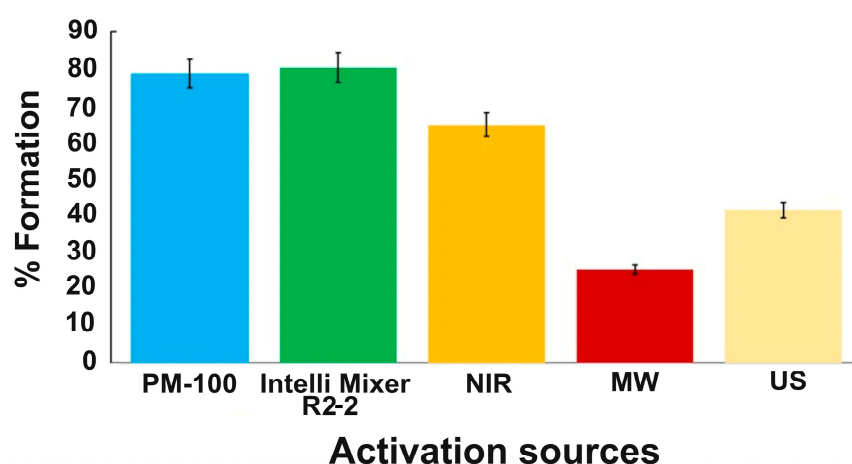


Figure 2. Comparative histogram of higher percent formation of DIM[®] among the different activation sources (Mean ± S.D.); according to the evaluation the results correspond to the mean of three independent events.

As can be seen in Figure 1, in general, the use of other non-conventional activation sources gave a minor percentage of formation; however, the NIR proceeded with the best formation percent (ca 64%) in comparison to MW and US (25 and 41%, respectively). In NIR mode are induced diverse vibrations of the chemical bonds: stretching, bending, rocking, and twisting, matching conveniently the absorption features of the reagent and solvent, substrate, and catalyst, thus, NIR absorbed by the mixture producing the essential heat to promote the reaction [6,7,69], this process provided better percent formation of target molecules than US or MW, but less than mechanochemical process. Related to the US activation of the reaction, the obtained results are attributed to cavitation-collapse effects; in this case, the collapse in the solid phase by micro drops of solvent produces ultrasonic low acceleration, endorsing low energy chemical reaction and consequently diminishing both the local heating, pressures and the heating and cooling rates. In addition, the micro drops at localized sites in the liquid mixture contain small amounts of dissolved gas, then where they burst release sufficient temperature and pressure to facilitate the reaction [70]. In the case of the MW activating mode, it could be disadvantaged due to a low polarity of

the reaction. In other words, the polarity stimulated by TAFF[®], acetone, which has a weak capability to transform electromagnetic energy into heat, due to loss tangent (tangent δ , 0.054), and the reactants were not sufficient for a good promotion of the reaction. In other words, the quantity of heat transferred to the reaction is lower to overcome the activation energy and complete the reaction quickly, generating poor formation percent (ca. 25 %) [69].

2.3. Statistically Significant Differences

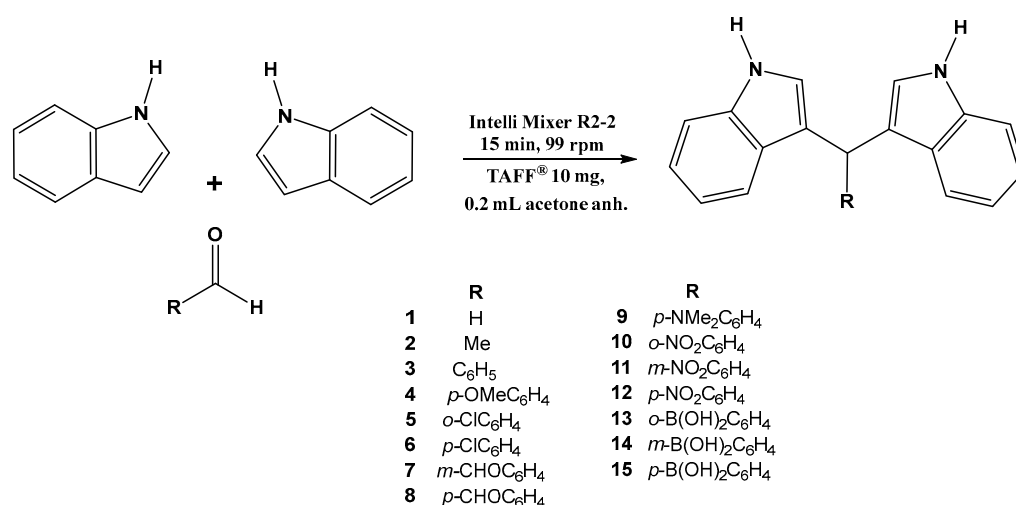
It is important to highlight that all the displayed results were supported by the analysis of variance (ANOVA) that showed statistically significant differences ($p < 0.05$) among all activation sources. Hence, the Analysis Tukey's test showed that between PM-100 and Intelli-Mixer R2-2 activation sources does not exist a statistically significant difference; consequently, the formation percent of DIM[®] is higher and comparable, 78.53 and 80.16%, respectively; but in contrast with all other activation sources, the formation percent of DIM[®] was diminished (Figure 2), displaying statistically significant differences among all of them.

2.4. Structural Attribution

The spectroscopic identification (EI-MS, HRMS-FAB⁺, ¹H NMR) and physical (mp) of DIM[®], were performed by correlating the data previously reported in the literature [28,71] with the experimentally obtained, DIM[®]: Red solid; mp: 166–168 °C; yield 75%; EI-MS (70 eV) m/z (% ra)[assignment]: 246(65)M⁺•, 245(50)[M-1]⁺, 130(93)[M-116]⁺•, 117(100)[M-129]⁺; HRMS-FAB⁺: precise 246.1147; exact 246.1157, −4.1 ppm error; unsaturations 12, consistent data for C₁₇H₁₄N; ¹H NMR (acetone-*d*₆) δ /ppm: 4.22 (CH₂, 2H, s); 6.95–7.11, (H-pyrrole, 2H, m); 7.35–7.59, AA'BB', (H-Aromatic, 8H, m); 9.95 (NH, 2H, s) (Figures S6 and S7), respectively.

2.5. Generalization by Intelli-Mixer R2-2 Mode to Produce Various DIMs

In the second part of this search, we decided to assess the generality of the mechanochemical approach, it was important to highlight the scarce availability of derivatives of I3C; hence, it was considered appropriate to perform the next stage employing several aldehydes as substrates and consequently establish a new contribution for the [KQ-3MCR] protocol. Thus, the goal in this part of the research was accomplished by the Intelli-Mixer R2-2 device, using TAFF[®] as the catalyst, and a green solvent (Scheme 2), the obtained results are summarized in Table 4.



Scheme 2. Reference [KQ-3MCR] protocol by Intelli Mixer R2-2/TAFF[®]/green solvent.

Table 4. DIMs production employing an Intelli Mixer R2-2 device ¹.

Product/ Reaction Time (h)	R	Yield (%)	mp (°C)	EI-MS
		Experimental/Literature	Experimental/Literature	M ⁺ • (% ra)
1/2	H	75/90 [72]	166–168/166–167 [72]	246 (89) [73]
2/1.5	Me	49/85 [71]	150–152/153–155 [71]	260 (10) [73]
3/0.7	C ₆ H ₅	90/75 [46]	123–125/125–127 [46]	322 (40) [26]
4/1.5	<i>p</i> -OMeC ₆ H ₄	39/70 [58]	190–192/191–193 [58]	352 (100) [41]
5/2	<i>o</i> -ClC ₆ H ₄	69/92 [46]	68–72/72–74 [74]	356 (100) [41]
6/1.5	<i>p</i> -ClC ₆ H ₄	68/96 [46]	76–80/76–77 [75]	356 (100) [41]
7/1.5	<i>m</i> -CHOC ₆ H ₄	75/94 [76]	190/176–178 [76]	350 (100) [76]
8/1.5	<i>p</i> -CHOC ₆ H ₄	83/85 [58]	201–203/203–204 [58]	350 (100) [76]
9/1.5	<i>p</i> -NMe ₂ C ₆ H ₄	46/55 [58]	168/166–168 [58]	365 [59] ²
10/1.5	<i>o</i> -NO ₂ C ₆ H ₄	93/80 [71]	70–75/70–72 [77]	367 (20) [77]
11/1	<i>m</i> -NO ₂ C ₆ H ₄	80/80 [71]	265/265–266 [58]	367 (20) [78]
12/1	<i>p</i> -NO ₂ C ₆ H ₄	70/85 [71]	223/221–223 [58]	367 (100) [41]
13/1	<i>o</i> -B(OH) ₂ C ₆ H ₄	53/46 [62]	141–144/141–146 [62]	366 [62] ²
14/1	<i>m</i> -B(OH) ₂ C ₆ H ₄	42/41 [62]	179–181/180–184 [62]	366 [62] ²
15/1	<i>p</i> -B(OH) ₂ C ₆ H ₄	42/61 [62]	187–193/190–195 [62]	366 [62] ²

¹ See materials and methods section; ² do not appear.

As can be seen in Table 4, the best yields were obtained when the aromatic ring-bearing electron drawing groups (NO₂, Cl, CHO) in comparison with electron-releasing groups (Me, NMe₂), showing a regular behavior, as a representative example, in **10** the *orto* position, the electrophilic character of the carbonylic carbon is expected to be higher for the electrophilic aromatic substitution.

To our knowledge, the obtained results are indicative of a new good contribution to the [KQ-3MCR] protocol since unequivocally a green approach is offered, according to the following advantages: microscale (Principle #1), high economy-3MCR (Principle #2), employing acetone a green solvent (Principle #5), mechanochemistry (Principle #6), the employment of a bentonitic clay, TAFF[®], a green catalyst [14,62,79–81], avoiding the use of toxic or expensive catalyst [41,46,71,73,74,77,78] (Principle #9), reaction monitoring (Principle #11). In addition to the convenient reaction yields, and the low reaction time, wishing to highlight that this procedure could be extrapolated to the “macroscale”, since appropriated mill equipment, already exists in the pharmaceutical industry [82–84]. Consequently, considering the principles’ incidence previously mentioned and using a convenient green metric (see references [21,68]), general greenness may be considered a good approach.

Regarding the identification of the target molecules, **1–15**, it was conveniently carried out, by correlating their EI-MS data with those previously published [62]; in general, the expected molecular ions (M⁺•) (Table 4), appeared with significant percentages of relative abundances also perceiving characteristic fragment-ions for each compound.

However, it is convenient to note that, for the three hybrid molecules (**13–15**), potential drugs due to their cytotoxicity [62], their identification was complemented by comparing their EI-MS (70 eV) data-no molecular ions detected, with FAB⁺-MS (6 eV) using thioglycerol as matrix (Figures S8–S13); during these determinations, several adducts produced between the boron atom of the target molecules and the sulfur residues of the matrix were detected; for example, Figure 3, its identification was unequivocally assessed by HRMS-FAB⁺, *m/z* 437 [M+C₃H₃S]⁺, precise 437.1489, exact 437.1495, +1.3 ppm error in agreement to C₂₆H₂₂N₂O₂BS (Figure S14).

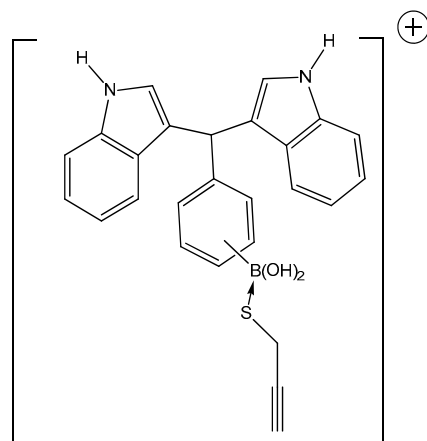


Figure 3. Typical adduct of 2-, 3-, and 4-(di(1*H*-indole-3-yl) methyl) phenylboronic acids.

3. Materials and Methods

3.1. General

The indole, indole-3-carbinol, and aldehydes were commercially acquired from Sigma-Aldrich (St. Louis, MO, USA) and were employed without purification. The bentonitic clay—of Mexican origin—used as the catalyst was acquired as Tonsil Actisil FF[®], commercialized by the chemical industry “Tonsil Mexicana S.A. de C.V.” (CDMX, México). The solvents *n*-hexane, EtOAc, and anhydrous acetone were technical grade and were used without further purification from Materiales y Abastos Especializados S.A. de C.V. (Zapopan, Jalisco, México). In general, the reactions were monitored by thin layer chromatography (TLC), using 60:40 of *n*-hexane-EtOAc as eluent, on percolated (0.25 mm) Merck silica-gel 60-F 254 aluminum sheets; the purification of the products was carried out by preparative chromatography (PC), using the previously established eluent for TLC, on percolated Merck silica-gel 60-F 254 glass sheets (Merck-Millipore, Darmstadt, Germany). In general, the product visualization was conducted using a 254 nm UV lamp (UVLS-24, Upland, CA, USA), I₂ vapors, or CeSO₄/H₂SO₄ 1%.

Melting points, uncorrected, were measured using a Fisher Scientific apparatus Scientific Serial No. 810N0220 (Cole-Parmer, IL, USA). The mass spectrometric identifications were performed by gas chromatography-mass spectrometry (GC-MS) under electronic ionization mode, using GC model 6850, G2630A/G3170A, and MS 5975C all Agilent (Santa Clara, CA, USA). GC was performed using a 5% phenylmethylsilicon column (30 m × 0.25 μm i.d., 0.25 μm film) HP-5MS. The linear velocity of the helium carrier gas was 1 mL/min. The injector temperature at 300 °C, the gradient program used was as follows: 40 °C T1, rate 8 °C/min, 300 °C T2, 4 min; the EI and HRMS-FAB⁺ measurements were made using a JEOL JMS-700 MStation mass spectrometer (JEOL, Tokyo, Japan) for HRMS-FAB by positive mode ionization (+) were performed at 25 °C, 6 KeV of FAB energy, 10 mA of emission current, and 10 kV of acceleration voltage, using Xe as the ionization gas and PEG (poly (ethylene glycol)) from 200 to 800 as internal reference at resolutions of 10,000, 20,000, 30,000, and 45,000. The accurate mass was calculated as the mean value of the data measured in 5–6 scans as determined from the top and centroid mass of the ion signals. The elemental compositions were calculated within a mass range of ±10 ppm from the measured accurate mass. For EI, we performed the process with a source temperature of 230 °C, ionization energy of 70 eV, and an ionization trap current of 100 μA. The corresponding NMR determinations were carried out using a Varian Mercury-300 (Palo Alto, CA, USA) at 300 MHz and 75 MHz for hydrogen and carbon nuclei, respectively, solvent acetone-*d*₆, and TMS as an internal reference.

The HSBM methodology was performed using a mechanical milling device: Retsch model PM 100 high-speed planetary stirring ball mill (Haan, Mettmann, Germany), using a cylindrical stainless-steel reactor whose dimensions are 30 mm in length and 30 mm in diameter, with a capacity of 12 mL, and six stainless steel balls of 0.9 cm of diameter. Daigger Scientific mixer, model Intelli-Mixer R2-2 (ELMI, Newbury Park, CA, USA), employing the vigorous mix mode with 20 mL stainless steel vessels and six stainless steel balls of 0.9 cm in diameter. Microwave experiments were performed using a CEM Focused Microwave Synthesis System; model Discover System (CEM, Matthews, NC, USA), Volts 90/140 VAC, max. microwave power 300 W. Near-infrared irradiation was employed in a commercial “Flavor-Wave Oven” (110 V/120 V-60 Hz | 1300 W) (FOSHAN, China). Ultrasound-assisted transformations were assessed with a Branson Ultrasonic Cleaner model 1510R-DTH, (117 V | 50–60 Hz | 160 W) (Branson Ultrasonic Corporation, Danbury, CT, USA).

3.2. Synthesis of DIM[®] Employing TCh-HSBM

3.2.1. Mortar/Pestle Procedure

Three independent experiments were conducted between indole (80 mg, 0.68 mmol), indole-3-il-carbinol (I3C) (100 mg, 0.68 mmol), and TAFF[®] (10 mg [62]), and were placed in an appropriate mortar and were ground during 4 h at room temperature. The percent formation and identification of DIM[®] were determined by GC-MS; unfortunately, this process in our hands required a large reaction time achieving low % formation (<10%) of the product.

3.2.2. HSBM Restch Model PM100 Device Procedure

Three independent experiments were conducted (for each point) and eight experimental conditions were tested to establish the best conditions; indole (80 mg, 0.68 mmol), indole-3-il-carbinol (I3C) (100 mg, 0.68 mmol), TAFF[®] (10 mg [62]), and 0.2 mL of anhydrous acetone as dispersant agent were placed in an appropriate stainless steel vessel with six stainless steel balls of 0.9 mm of diameter: (1) 30 min/100 rpm; (2) 30 min/200 rpm; (3) 30 min/300 rpm; (4) 30 min/400 rpm; (5) 60 min/100 rpm; (6) 60 min/200 rpm; (7) 60 min/300 rpm; (8) 60 min/400 rpm (Scheme 1, Table 2a,b). The percentage formation and identification of DIMs were determined by GC-MS.

3.2.3. Intelli-Mixer R2-2 Device Procedure

Three independent experiments were conducted (for each point) and four experimental conditions were tested to establish the best conditions; indole (80 mg, 0.68 mmol), indole-3-il-carbinol (I3C) (100 mg, 0.68 mmol), TAFF[®] (10 mg [62]), and 0.2 mL of anhydrous acetone as dispersant agent were placed in an appropriate stainless steel vessel with six stainless steel balls of 0.9 mm of diameter: (1) 15 min/25 rpm; (2); 15 min/50 rpm; (3) 15 min/75 rpm; (4) 15 min/99 rpm (Scheme 1, Table 2c). The percentage formation and identification of DIM[®] were determined by GC-MS.

3.3. Production of DIM[®] by Comparison of Other Non-Conventional Activating Reaction Modes

Each achieved result corresponds to the mean of three independent events for each one of the compared procedures. Three experimental conditions were tested: (1) indole (80 mg, 0.68 mmol), indole-3-il-carbinol (I3C) (100 mg, 0.68 mmol), TAFF[®] (10 mg [62]), and 0.2 mL of anhydrous acetone; (2) indole (80 mg, 0.68 mmol), indole-3-il-carbinol (I3C) (100 mg, 0.68 mmol), TAFF[®] (10 mg [62]); (3) indole (80 mg, 0.68 mmol), indole-3-il-carbinol (I3C) (100 mg, 0.68 mmol), and 0.2 mL of anhydrous acetone. Thus, for the NIR source, the reaction time was 30 min at 135 °C, for the MW source was 5 min reaction at 100 °C, with 100 W of power, and for the US method, the reaction time was 30 min at 40 °C, with 60 Hz

of frequency. For this last method, it is important to mention that *n*-hexane was employed instead of acetone due to acetone being evaporated (Table 3).

3.4. DIMs Production Employing Intelli-Mixer R2-2 Device

Each result data corresponds to the mean of three independent events. Employing a Intelli-Mixer R2-2 device, were placed in an appropriate stainless steel vessel with six stainless steel balls of 0.9 mm of diameter during 15 min of reaction at a frequency of 99 rpm, the substrate indole (235 mg, 2.006 mmol) in the presence of TAFF[®] (10 mg [62]), 0.2 mL of anhydrous acetone as dispersant (green solvent) was mixed employing 15 different carbonylic reagents: [formaldehyde (30 mg, 0.999 mmol), acetaldehyde (45 mg, 1.022 mmol), benzaldehyde (275 mg, 1.002 mmol), 4-methoxybenzaldehyde (136 mg, 0.998 mmol), 2-chlorobenzaldehyde (141 mg, 1.003 mmol), 4-chlorobenzaldehyde (141 mg, 1.003 mmol), 4-acetylbenzaldehyde (149 mg, 1.006 mmol), 3-acetylbenzaldehyde (149 mg, 1.006 mmol), 4-(dimethylamine)benzaldehyde (150 mg, 1.005 mmol), 2-nitrobenzaldehyde (152 mg, 1.006 mmol), 3-nitrobenzaldehyde (152 mg, 1.006 mmol), 4-nitrobenzaldehyde (152 mg, 1.006 mmol), (2-formylphenyl)boronic acid (150 mg, 1.000 mmol), (3-formylphenyl)boronic acid (150 mg, 1.000 mmol) or (4-formylphenyl)boronic acid (150 mg, 1.000 mmol)]. According to Scheme 2 and Table 4.

3.5. Optional Studies Involving Different Green Solvents

Between the common organic green solvents (acetone, ethyl acetate, ethyl and methyl butanoates, acetone, and water), acetone resulted the best; however, it is convenient to note that there are many types of green solvents like: ionic liquids, supercritical fluids, water, and supercritical water, fluorinated hydrocarbons, polyethylene glycol-polyols, ethyl lactate (many natural esters), in addition to a great number of monoterpenes, between many other. Consequently, several appropriate studies could be implemented selecting convenient groups (kinds) of green solvents.

3.6. Potential Improvements, Large-Scale Optimization, or Applications in Other Reactions

It is important to highlight that in 2019, the IUPAC proposed mechanochemistry as a top ten emerging technology in chemistry, moreover many years ago it was considered a paradigm-shifting method for conducting chemical reactions [9,10,85–88]. However, for the near future next decade, it is a priority to increase the central knowledge of mechanochemical reactions to be able to discern when mechanochemical conditions are preferable over recognized approaches (mantle heating, ultrasound, microwave, and infrared electromagnetic irradiation, and some others). It is very important to note that the prediction of chemical reactivity under mechanochemical conditions is an area of continuous expansion, with many controlling theories to be discovered. In addition, a crucial viewpoint for the development of mechanochemistry is the innovation of regulated milling equipment. Mechanochemistry has the potential to revolutionize many industrial applications, such as energy, nanomaterials, and environmental remediation. By using mechanochemistry, our industry can potentially reduce its costs, waste, and environmental impact, while increasing its efficiency, quality, and innovation. Mechanochemistry can also enable the discovery of new compounds and mechanisms that are inaccessible by conventional methods; in summary, mechanochemistry certainly is an excellent key of actuality for industrial applications, as it offers a simple, efficient, and versatile way to manipulate matter at the molecular level [89].

3.7. Statistical Process Control

Analysis of variance was performed using the ANOVA procedure. Tukey's test was used to determine the differences in means and the significance of differences was

evaluated at the $p < 0.05$ level. Data analysis was carried out using Statgraphics Centurion XVI software, version 16.2.04 (64-bit) 1982–2013, StatPoint Technologies, Inc., Warrenton, VA, USA.

4. Conclusions

“The UNESCO-request to educate in sustainable development and the ACS GCI Pharmaceutical Roundtable”, were addressed attending the Green Chemistry Protocol (12 Principles) to produce DIM[®], being convenient to highlight the occurrence of: *Principle #2*-atomic economy a 3MCR, *Principle #5*-use of acetone a green reaction-medium, *Principle #6*-energy efficiency using TCh-HSBM in comparison to US, NIR, and MW as activating reaction modes, *Principle #9*-Use of TAFF[®] bentonite as the catalyst, and *Principle #11*-monitoring the reaction by GC-MS. In addition, there is a slight contribution to the corresponding reaction mechanism validating the presence of the main product intermediate (I3C). Once the reaction conditions were considered suitable to obtain the DIM[®], they were employed to perform a generalization by TCh-HSBM for the KQ-3CR protocol. Finally, it is convenient to highlight that the TCh-HSBM, is an important approach to performing novel organic transformations, and moreover it certainly is an excellent key of actuality for industrial applications, as it offers a simple, efficient, and versatile way to manipulate matter at the molecular level procedure has the viability to be extrapolated to “macro-scale” since appropriated mill-equipment already exists in the pharmaceutical industry.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/catal15030238/s1>, Figure S1a: TIC chromatogram of DIM[®] employing the Intelli-Mixer R2-2 device; Figure S1b: Mass spectrum of DIM[®] employing the Intelli-Mixer R2-2 device; Figure S2a: TIC chromatogram of DIM[®] employing the PM-100 device; Figure S2b: Mass spectrum of DIM[®] employing the PM-100 device; Figure S3a: TIC chromatogram of DIM[®] employing NIR; Figure S3b: Mass spectrum of DIM employing NIR; Figure S4a: TIC chromatogram of DIM[®] employing US; Figure S4b: Mass spectrum of DIM[®] employing US; Figure S5a: TIC chromatogram of DIM[®] employing MW; Figure S5b: Mass spectrum of DIM[®] employing MW; Figure S6: ¹H NMR (Acetone-*d*₆) of DIM[®]; Figure S7: EI-MS (70 eV) of DIM[®]; Figure S8: EI-MS (70 eV) of 2-(di(1*H*-indole-3-yl)methyl)phenylboronic acid; Figure S9: FAB⁺ (6 eV) of 2-(di(1*H*-indole-3-yl)methyl)phenylboronic acid; Figure S10: EI-MS (70 eV) of 3-(di(1*H*-indole-3-yl)methyl)phenylboronic acid; Figure S11: FAB⁺ (6 eV) of 3-(di(1*H*-indole-3-yl)methyl)phenylboronic acid; Figure S12: EI-MS (70 eV) of 4-(di(1*H*-indole-3-yl)methyl)phenylboronic acid; Figure S13: FAB⁺ (6 eV) of 4-(di(1*H*-indole-3-yl)methyl)phenylboronic acid; Figure S14: FAB⁺ (6 eV) of adduct between thioglycerol and 2-(di(1*H*-indole-3-yl)methyl)phenylboronic acid.

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Abbreviations

The following abbreviations are used in this manuscript:

UNESCO	United Nations Educational, Scientific, and Cultural Organization
DIM [®]	Diindolylmethane
GCh	Green Chemistry
DESD	Decade to Educate for a Sustainable Development
SD	Sustainable Development
NIR	Near
MW	Microwave-irradiation
US	Sonochemistry
MCh	Mechanochemistry
TCh	Tribochemistry
HSBM	High-Speed Ball Milling
TAFF [®]	Tonsil Actisil FF
I3C	indole-3-carbinol
MCR	Multicomponent Reaction
KQ-3MCR	Kamal Quereschi–Three Multicomponent Reaction
GC-MS	Gas Chromatography–Mass Spectrometry
EI-MS	Electron Ionization–Mass Spectrometry

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