A Platinum Open Access Journal for Organic Chemistry

Paper

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DOAJ Seal

Arkivoc **2021**, part viii, 242-252

Microwave-assisted synthesis of novel 1-{[(diindolyl)methyl]benzyl}-2-{[(diindolyl)methyl]phenyl}-1*H*-benzimidazole scaffold via two-consecutive multicomponent reactions

Ricardo Alfredo Luna-Mora,[a] Cecilio Álvarez-Toledano,[b] Hulme Rios-Guerra,[a] Fernando Ortega-Jiménez,[a] José Guadalupe López-Cortés,[b] Javier Pérez-Flores,[b] Ángeles Torres-Reyes,[a] Lessly Moreno-González,[a] Alejandro Martínez Zaldívar,[a] Francisco Barrera-Téllez,[a] José Guillermo Penieres-Carrillo*[a]

[a] Sección de Química Orgánica. Facultad de Estudios Superiores Cuautitlán-UNAM, Campo 1. Avenida 1. de Mayo s/n, Cuautitlán Izcalli, C.P. 54740, Estado de México, México

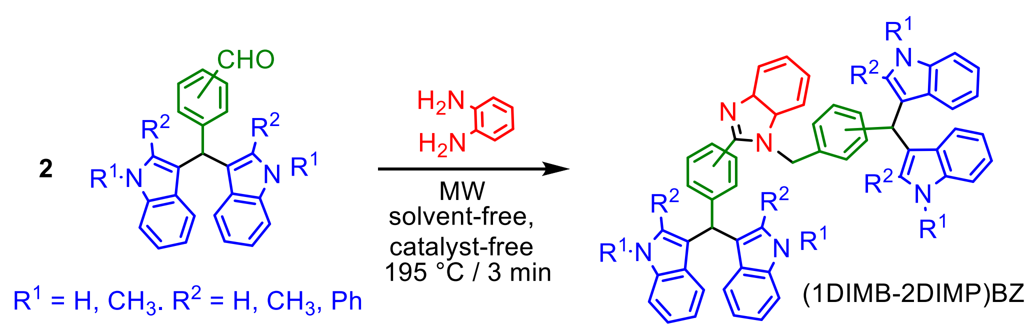
[b] Instituto de Química UNAM, Circuito Exterior, Ciudad Universitaria, Coyoacán C.P. 04510, Cuidad de México, México

Email: penieres@unam.mx

Received 12-14-2020 **Accepted** 05-06-2021 **Published on line** 06-13-2021

Abstract

An efficient microwave synthesis of 1-{3- or 4-[bis(1*H*-indol-3-yl)methyl]benzyl}-2-{3- or 4-[bis(1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole derivatives was achieved. This novel azaheterocyclic hybrid scaffold was assembled in excellent overall yield through two-consecutive ABB-type 3CR design by the reaction of (3- or 4-formylphenyl)diindolylmethanes, synthesized from a mixture of isophthalaldehyde or terephthalaldehyde, respectively, 1*H*-indole or derivatives, and *ortho*-phenylenediamine. The use of microwave technology, catalyst-free, and solvent-free conditions, as well as the avoidance of time-consuming and tedious workup procedure, make it an appealing method to access a novel (1DIMB-2DIMP)BZ scaffold endowed with potential biological activity.



Keywords: Benzimidazoles, diindolylmethanes, aryldialdehydes, *o*-phenylenediamine, microwave energy.

Introduction

It is known that natural scaffolds containing either bis(indolyl)methane or benzimidazole core have been considered biologically relevant in the search of new potential applications as candidates with pharmaceutical activity.[1-5]

Even though indole-3-carbinol **1** and their metabolic products such as 3,3´-diindolylmethane (DIM) **2** and the oligomers **3**-**4** have shown renewed anticancer properties;[6,7] another naturally occurring indole alkaloids featuring a central azaheterocyclic core decorated with either 1*H*-indol-3-yl or bis(1*H*-indol-3-yl)methane moieties have gained a prominent position as promising cytotoxic, antifungal and antibiotic agents with innovative mechanism of action.

Among the various structural classes highlight Hamacanthin **5**, isolated from marine sponges *Spongosorites sp*, which is a 5,6-dihydropyrazin-2(1*H*)-one with two-indolyl molecular units.[8] But more importantly, it has been noted that replacement of functionals groups or structural contraction of the azaheterocyclic ring, as in Tulongicin **6**, the biological activity significatively is affected. In this regard, the 4,5-dihydro-1*H*-imidazole core attached to the bis(indolyl)methane structural unit specifically acts as an antimicrobial agent that inhibits the growth of *S. aureus* (Figure 1).[9] In the same way, synthetic compounds such as indolo[2,3-b]quinoline derivatives **7** and chromeno[2,3-b]indole derivatives **8** highly promising as anti-MRSA agents.[10]

Regarding the DIM core, it has been proposed as a relevant building block in the pursuit of highly functionalized indole derivatives.

Despite this important breakthrough, significant synthetic challenges remain to be solved in the synthesis of structurally elaborated and diverse heterocyclic-DIM molecules.

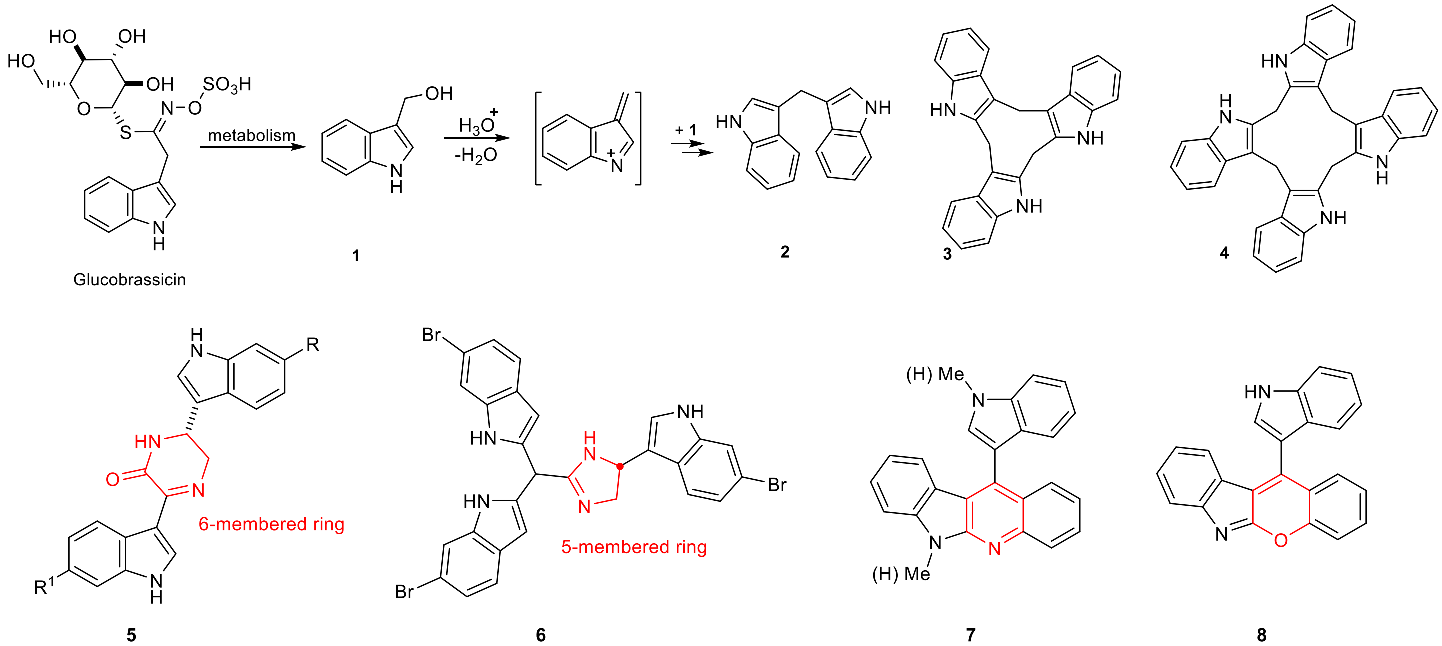


Figure 1. Products of metabolic transformation **2**–**4** of indolyl-3-carbinol **1** and selected natural **5**–**6** and synthetic **7**–**8** compounds featuring indolyl motif with prominent bioactivity.

Therefore, in the search of a new synthetic design for creating molecular complexity and diversity with maximum simplicity, multicomponent reactions (MCR) have been ideally considered the best choice owing to their intrinsic green character, great exploratory power, and economic advantages over the orthodox multi-step synthesis.[11-14]

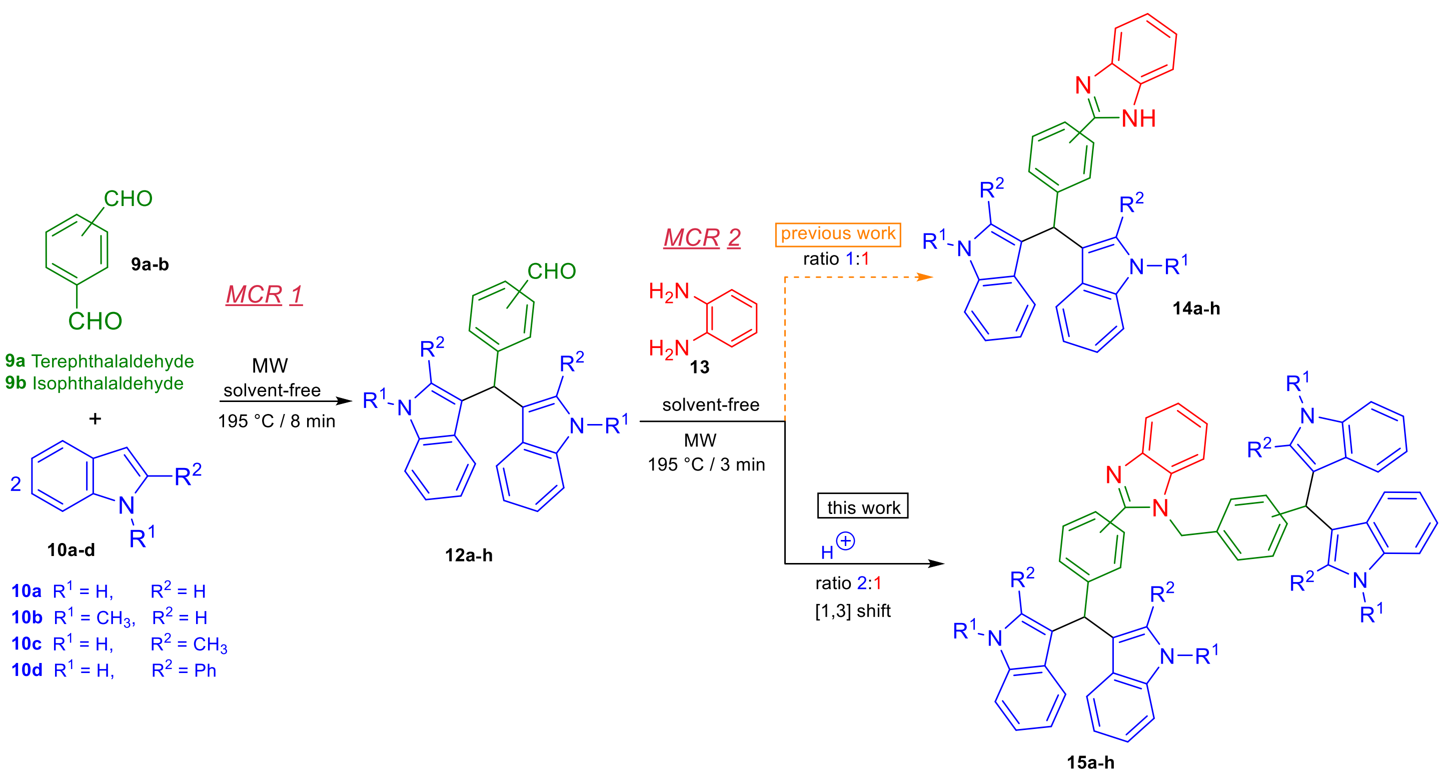
Benzimidazole is an important structural core in pharmaceutical chemistry, where it has been used in antitumor,[15] antiparasitic,[16] antimicrobial,[17] and antihistaminic agents.[18] Benzimidazole derivatives with short peptide sequences have antidiabetic, antibiofilm, and antioxidant activities.[19]

Additionally, some complexes with metals such as cobalt(II) and zinc(II) and coordinated to benzimidazole bearing 1-benzyl and 2-phenyl moieties have shown effective anticancer activity,[20] and some organophosphorus-benzimidazole compounds have potential pesticidal activity.[21]

Benzimidazole derivatives have been usually synthesized by classical cyclocondensation of *o*-phenylenediamines with the corresponding carboxylic acids[22] or from aldehydes under oxidative conditions with some reagents such as sodium metabisulfite[23,24] or nitrobenzene[25].

In this way, we recently reported the synthesis of 2-(3 or 4-(bis(1*H*-indol-3-yl)methyl)phenyl)-1*H*-benzimidazole derivatives (**14a–h**, Scheme1), with the use of microwave energy source in both catalyst-free and solvent-free conditions, with excellent overall yields and short reaction times.[26]

Encourage with these results, in this communication we report two-consecutive multicomponent reactions of ABB-type (3CR)[27,28] to achieve the formation of 1-{3- or 4-[bis(1*H*-indol-3-yl)methyl]benzyl}-2-{3- or 4-[bis(1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole derivatives (**15a–h**, Scheme 1), named (1-DIMB-2DIMP)BZ, from two equivalents of **12a-h** and one equivalent of *o*-phenylenediamine **13**.

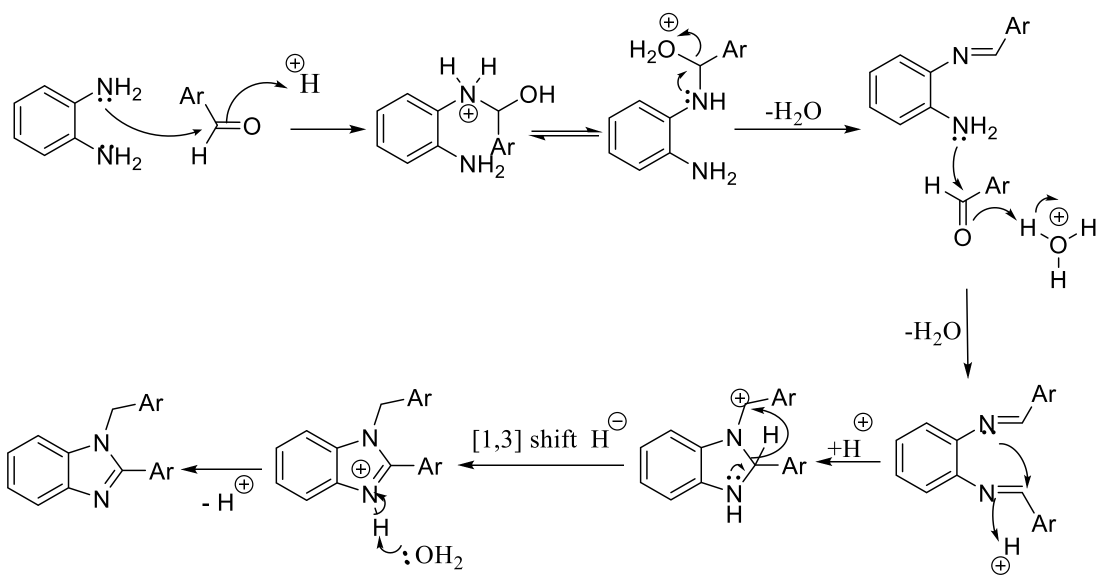


Scheme 1. Synthesis of **15a-h** based on a two-consecutive multicomponent reaction approach.

Results and Discussion

To assembling the more elaborated and sterically congested scaffold **15a**–**h** it was devised from a two-consecutive ABB-type 3CR design based on the incorporation of 4-(bis(1*H*-indol-3-yl)methyl)benzaldehyde derivatives **12a**–**h** as key reactants in a subsequent post-multicomponent step. These target building blocks were selectively prepared by reacting 2 mmol of 1*H*-indole **10a** or its derivatives **10b**–**d** with 1 mmol of either isophthalaldehyde or terephthalaldehyde **9a**–**b** under microwave irradiation following the conditions outlined in Scheme 1-MCR 1. In our hands, all eight synthesized 3,3´-DIMs **12a**–**h** was obtained in excellent yield (91-96 %).

For the syntheses of the target molecules **15a-h**, in a first instance, it is important to mention that the *ortho* isomers of **12a-h** did not react with **13** at the used reaction conditions to give the corresponding target molecules, what is attributed to the great steric effect presented. So, taking into account that the pattern of substitution of the starting reagents **12a–h** (that is 1,3 or 1,4) may exert a notable influence on the efficiency of transformation of the reaction, we initially re-explored the synthesis of the sterically least hindered substrate with *para* substitution **12a** and *o*-phenylenediamine **13** in 1:1 molar ratio. Such findings assume the transitory formation of a double Schiff base as the key intermediate from which evolve the formation of the 2-substituted benzimidazole **14a** as the thermodynamic more stable product after undertaking a 5-*exo*-trig ring closure and subsequent aromatization, as we reported previously. So, when the experiment was conducted in a 2:1 molar ratio, product **15a** was successfully obtained in 85 % yield by an intramolecular 1,3-hydride migration as the final step in the proposed reaction mechanism, Scheme 2, whereas the 2-substituted benzimidazole **14a** was isolated in only 8 % yield as a byproduct (Table 1, entry 1).



Scheme 2. Proposed mechanism for the formation of 1,2-disubstituted benzimidazoles.

Although the success of this kind of reaction has been documented elsewhere in presence of a well-tailored organometallic catalyst as well as employment of trimethylsilyl chloride in an aqueous medium, this outcome evidence that comparable efficiency and can be achieved using microwave irradiation in absence of catalytic agents.[29-32]

IR, ^{1}H, ^{13}C NMR spectroscopy, and HRMS analysis confirmed the structural attributes of compound **15a**. Briefly, the key methylene moiety deduced from the intramolecular 1,3-hydride migration tethered to *N*-1 of the imidazole skeleton appears as singlet signal at 6.43 ppm in the ^{1}H NMR spectra, whereas the two signals occurring at 52.4 and 153.6 ppm in the ^{13}C NMR spectra were attributed to *N*CH_2- and C-2 of the imidazole ring, respectively.

Inspired by the above findings, we set out to explore the scope and efficiency of the reaction by using several 1,4- and 1,3-diindolylmethanearenecarbaldehydes **12b–h**. Table 1 shows the results obtained by the microwave effect, highlighting that neither substituent effects (H, Me, Ph on *N*-1 and C-2) nor the steric factors derived from the pattern of substitution of the bis(indolyl)methane motif and the arenecarbaldehyde moiety noticeably affect the selectivity and overall yield of all synthesized target products **15b–h**. In this regard, we found that the more sterically demanding 1-{3-[bis(2-phenyl-1*H*-indol-3-yl)methyl]benzyl}-2-{3-[bis(2-phenyl-1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole **15h** is obtained in excellent yield (Table 1, entry 8), comparable with the outcomes delivered in the synthesis of the least sterically demanding azaheterocycle compound **15a** (Table 1, entry 1).

Therefore, the logical inference from these findings suggests that the structural complexity level of the arenecarbaldehyde derivative used as starting reactive has no significant detrimental effect on the efficiency and rate of reaction.

Table 1. Assembling of **15a-h** by catalysis-free ABB-type three multicompound reaction.

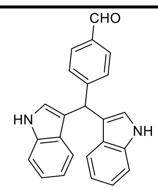
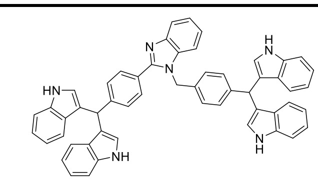
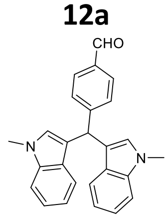
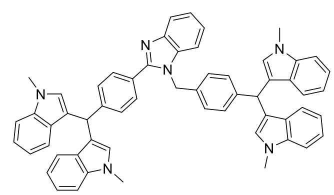
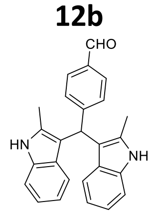
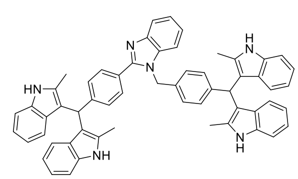
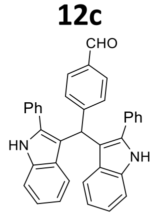
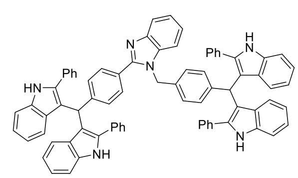
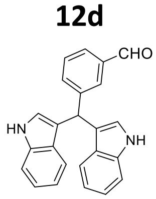
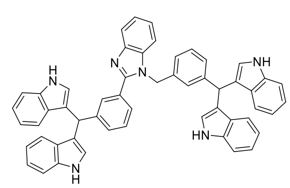
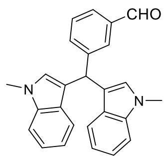
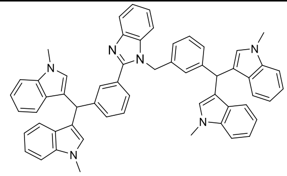
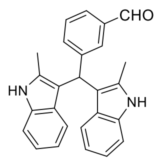
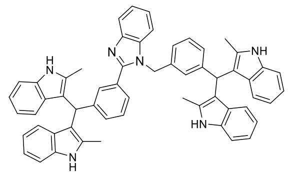
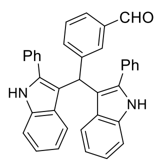
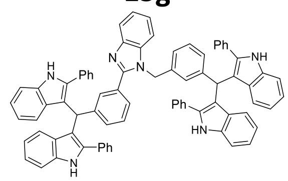
Entry	**12**	Product	m.p. (°C)	Yield (%)[c]
1	 **12a**	 **15a**	251-253	85 (8)
2	 **12b**	 **15b**	238-240	80 (12)
3	 **12c**	 **15c**	247	80 (9)
4	 **12d**	 **15d**	229-231	78 (10)
5	 **12e**	 **15e**	201-203	82 (9)

Table 1. Continued

6	 **12f**	 **15f**	196-198	83 (11)
7	 **12g**	 **15g**	203-205	89 (ND)[a]
8	 **12h**	 **15h**	189	83 (9)

[a]No determined

Conclusions

It was shown that the synthesis of (1DIMB-2DIMP)BZ from a two-consecutive multicomponent 3CR approach can be selectively promoted by the microwave effect, in short reaction times. Its operational simplicity and low environmental load combined with its excellent yields, broad substrate scope, and high efficiency of reaction achieved under catalyst-free and solvent-free conditions open a new way to synthesize bis(1,2-indolyl derivatives)benzimidazole molecules with potential biological interest.

The use of microwave technology, catalyst-free and solvent-free conditions, as well as avoiding tedious workup procedure, make it an appealing method to access novel (1DIMB-2DIMP)BZ scaffold endowed with potential biological activity.

Experimental Section

General. All microwave-assisted organic reactions were carried out using a monowave 300 Microwave Synthesis Reactor by Anton Paar. The reaction temperature was monitored with an immersing ruby thermometer. Melting points were determined on a Buchi B-450 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian EM-390 (300 MHz) instrument in $CDCl_3$ or DMSO-*d6,* and chemical shifts (δ) are given in ppm relative to TMS. Mass spectrometry (FAB^+) was measured on a JEOL JMS-SX102A mass spectrometer. IR spectra were recorded on a Perkin-Elmer 283B spectrophotometer using ATR techniques. All reagents, as well as solvents, were acquired from Aldrich without any treatment from its commercial presentation.

Typical procedures. The syntheses of **14a-h** were reported previously.[23] The experimental procedure for **14a** was: A mixture of (formylphenyl) diindolylmethane **12a** (1.4251 mmol, 0.4987 g) and *o*-phenylenediamine **13**

(1.4251 mmol, 0.1539 g), were thoroughly blended in a 20 mL microwave vial, pressure sealing and exposed to irradiation in a monowave 300 microwave reactor at 195 °C for 3 min. The solids formed were purified by preparative chromatography on silica gel using an eluting system of hexane/ethyl acetate (7:3) and recrystallized from ethanol-water.[15]

General procedure for the synthesis of (1DIMB-2DIMP)BZ (**15a–h**). A mixture of 3(or 4)- formylphenyl)diindol-3-ylmethane **12a–h** (2.00 mmol, 0.7000 g for 1*H*-indole, 0.7560 g for 1*H*-methylindole, 0.7560 g for 2-methyl-1*H*-indole and 1.004 g for 2-phenyl-1*H*-indole) and *o*-phenylenediamine **13** (1.00 mmol, 0.2160 g) were thoroughly blended in a 20 mL microwave vial, pressure sealing and exposed to irradiation in a monowave 300 microwave reactor at 195 °C for 3 min (the progress of the reaction was monitored by TLC).

After cooled at room temperature, the crude reaction was poured into ice-water and it was left stirring for 5 minutes. The resulting suspension was filtered, dried, and eventually purified by preparative chromatography using an eluting system a mixture of Hex/AcOEt (6:4). After carefully scraping the spots on the silica plate, the main detected product was extracted with hot ethanol, filtered, and dried to afford the spectroscopy pure compounds **15a–h**.

1-{4-[Bis(1*H*-indol-3-yl)methyl]benzyl}-2-{4-[bis(1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole (15a). Light pink powder (0.655 g, 85%). mp 251-253 °C. IR (Solid, ATR, vmax, cm^{-1}) 3380 (w), 3291 (br), 2916 (s), 2849 (m), 1618 (m), 1464 (m), 1217 (s), 743 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.07 (2H, s, 2CH, Methine), 6.43 (2H, s, CH_2, Methylene), 6.89 (4H, t, $^3J_{HH}$ 6 Hz, CH Indole), 6.99-7.06 (4H, q, $^3J_{HH}$ 9 Hz, CH Indole), 7.09-7.16 (8H, m, CH Indole); 7.22 (2H, s, CH Benzyl); 7.34-7.48 (8H, m, 4CH Indole, 2CH Benzimidazole, 2CH Benzyl); 7.54-7.56 (6H, m, 4CH Phenyl, 2CH Benzimidazole); 10.69 (1H, s, NH), 10.82 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 41.9 (CH_2 Methylene), 52.4 (CH Methine), 111.1 (CH Indole), 112.0 (CH Indole), 118.7 (CH Benzimidazole), 119.1 (CH Indole), 119.3 (CH Indole), 119.6 (CH Benzimidazole), 121.8 (CH Indole), 123.3 (CH Indole), 125.6 (CH Phenyl), 127.1 (CH Benzyl), 127.4 (CH Indole), 127.6 (CH Phenyl), 128.8 (CH Benzyl), 129.6 (CH Phenyl), 134.7 (CH Benzyl), 135.6 (CH Benzyl), 136.8 (CH Indole), 137.8 (CH Benzimidazole), 138.2 (CH Phenyl), 142.2 (CH Benzimidazole), 153.5 (CH Benzimidazole). HRMS (FAB+) *m/z* observed: 772.3310; C54H40N6 [M]+ Required: 772.3314.

1-{4-[Bis(1-methyl-1*H*-indol-3-yl)methyl]benzyl}-2-{4-[bis(1-methyl-1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole (15b). Dark pink powder (0.6624 g, 80%). mp 238-240 °C. IR (Solid, ATR, vmax, cm^{-1}) 3191 (br), 2918 (m), 2850 (m), 1465 (m), 1211 (s), 1062 (m), 986 (m), 805 (s), 741 (s), 580 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.47 (12H, s, 4CH_3, Methyl), 6.59 (2H, s, 2CH, Methine), 6.78 (2H, s, CH_2, Methylene), 7.65 (4H, s, CH Indole), 7.71-7.76 (6H, m, 4CH Indole, 2CH Benzyl), 7.90-7.95 (6H, m, 2CH Benzyl, 2CH Benzimidazole, 2CH Phenyl), 8.04-8.23 (m, 6H, 4CH Indole, 2CH Phenyl), 8.35-8.41 (m, 4H, 4CH Benzimidazole), 8.61 (d, 2H, 2CH Phenyl), 8.90 (d, 4H, 4CH Indole). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 30.1 (4CH3, Methyl), 56.1 (CH2, Methylene), 60.8 (2CH, Methine), 110.4 (CH Indole), 111.7 (4CH Indole), 118.0 (C Indole), 118.5 (4CH Indole), 119.6 (CH Benzimidazole), 119.8 (CH Benzimidazole), 122.0 (4CH Indole), 122.3 (4CH Indole), 124.0 (2CH Benzimidazole), 124.7 (2CH Phenyl), 125.5 (4CH Indole), 127.0 (2CH Benzyl), 127.6 (4C Indole), 128.2 (2CH Benzyl), 130.0 (2CH Phenyl), 131.9 (C Benzyl), 132.2 (C Benzyl), 135.0 (C Indole), 135.1 (C Phenyl), 135.4 (C Benzimidazole), 135.4 (C Phenyl), 145.3 (C Benzimidazole), 151.2 (C Benzimidazole). HRMS (FAB+) *m/z* observed: 828.3936; C58H46N6 [M]+ Required: 828.3940.

1-{4-(Bis[2-methyl-1*H*-indol-3-yl)methyl]benzyl}-2-{4-[bis(2-methyl-1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole (15c). Purple powder, (0.6624 g, 80%). mp 247 °C. IR (Solid, ATR, vmax, cm^{-1}) 3391 (w), 2917 (m), 2850 (m), 1687 (w), 1599 (w), 1456 (m), 1216 (s), 1014 (m), 993 (m), 825 (m), 739 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.18 (12H, s, CH_3), 4.75 (2H, s, Methine), 5.90 (2H, s, Methylene), 6.72-6.83 (8H, m, 8CH Indole), 6.88-6.95 (4H, m, 4CH Indole), 7.07 (2H, s, CH Benzimidazole), 7.21 (4H, d, 4CH Benzyl), 7.39 (2H, d, $^4J_{HH}$ 6 Hz, CH Phenyl), 7.73-7.88 (4H, m, 4CH Indole), 8.41-8.52 (2H, m, CH Benzimidazole), 8.89-9.03 (2H, d, $^4J_{HH}$ 12 Hz, 2CH Phenyl), 10.73 (4H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.7 (4CH_3, Methyl), 49.5 (CH_2, Methylene), 58.3 (CH, Methine), 109.5 (4CH, Indole), 116.8 (C Indole), 117.4 (4CH Indole), 118.2 (2CH Benzimidazole), 118.4 (2CH Benzimidazole), 121.0 (4CH Indole), 121.9 (4CH Indole); 123.6 (2CH), 126.3 (2CH Phenyl), 126.7 (2CH Benzyl), 126.9 (4C Indole), 127.6 (2CH Benzyl), 127.9 (2CH Phenyl), 128.7 (C Benzyl), 132.9 (C Benzyl), 134.4 (C Indole), 136.9 (C Indole), 138.9 (C Benzimidazole), 140.3 (C Phenyl), 142.3 (C Benzimidazole), 151.3 (C Imidazole). HRMS (FAB+) m/z observed: 828.3932; C58H46N6 [M]+ Required: 828.3940.

1-{4-[Bis(2-phenyl-1*H*-indol-3-yl)methyl]benzyl}-2-{4-[bis(2-phenyl-1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole (15d). White powder, (0.8392 g, 78%). mp 229-231 °C. IR (Solid, ATR, vmax, cm^{-1}) 3385 (br), 3208 (br), 3058 (m), 1619 (m), 1597 (m), 1502 (m), 1453 (m), 1277 (w), 743 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 5.51 (2H, s, Methylene), 5.81 (2H, s, 2CH, Methine), 6.82-6.89 (8H, m, 8CH Indole), 7.01-7.06 (6H, m, 4CH Benzyl, 2CH Benzimidazole), 7.23-7.36 (28H, m, 4CH Indole, 2CH Benzimidazole, 22CH Phenyl), 7.83-8.09 (4H, m, 4CH Indole), 8.13 (2H, d, $^4J_{HH}$ 6 Hz, 2CH Phenyl), 10.81 (4H, s, 4NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 41.3 (CH_2, Methylene), 52.8 (CH, Methine), 108.3 (4C, Indole), 111.5 (4CH Indole), 118.7 (4CH Indole), 119.4 (2CH Benzimidazole), 119.5 (2CH Benzimidazole), 119.7 (4CH Indole), 121.0 (4CH Indole), 123.3 (4C Indole), 125.7 (2CH Phenyl), 127.0 (8CH Phenyl), 127.3 (4C Indole), 127.4 (2CH Benzyl), 127.8 (4CH Phenyl), 128.6 (2CH Benzyl), 128.8 (2CH Phenyl), 129.6 (8CH Phenyl), 133.3 (4C Phenyl), 134.3 (C Benzyl), 135.2 (C Benzyl), 136.4 (4C Indole), 137.4 (C Benzimidazole), 138.7 (C Phenyl), 142.6 (C Benzimidazole), 153.5 (C Benzimidazole). HRMS (FAB+) *m/z* observed: 1076.4570; C78H56N6 [M]+ Required: 1076.4566.

1-{3-[Bis(1*H*-indol-3-yl)methyl]benzyl}-2-{3-[bis(1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole (15e). White powder (0.6322 g, 82%). mp 201-203 °C. IR (Solid, ATR, vmax, cm^{-1}) 3194 (w), 2954 (w), 2918 (m), 2850 (m), 1732 (w), 1465 (m), 1211 (s), 1062 (m), 986 (m), 805 (s), 741 (s), 580 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 5.75 (2H, s, 2CH Methine), 5.99 (2H, s, CH_2, Methylene), 6.75 (4H, s, CH Indole), 6.81-6.90 (10H, m, 8CH Indole, 2CH Benzyl), 7.01-7.08 (10H, m, 8CH Indole, CH Benzyl, CH Phenyl), 7.21-7.26 (6H, m, 4CH Benzimidazole, CH Phenyl, CH Benzyl); 7.53 (1H, d, $^4J_{HH}$ 3 Hz, CH Phenyl), 7.73 (1H, t, $^3J_{HH}$ 6 Hz, CH Phenyl), 10.76 (2H, d, 2NH), 10.89 (2H, d, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 53.0 (CH_2 Methylene), 58.2 (CH Methine), 111.0 (4CH Indole), 112.0 (4C Indol), 115.1 (4CH Indole), 118.8 (CH Benzimidazole), 119.1 (CH Benzimidazole), 119.5 (4CH Indole), 120.6 (2CH Benzimidazole), 122.5 (4CH Indol), 122.9 (CH Phenyl), 124.4 (CH Benzyl), 125.7 (CH Benzyl), 126.7 (4C Indole), 127.7 (CH Benzyl), 128.3 (CH Phenyl), 128.4 (CH Phenyl), 130.3 (CH Phenyl), 130.7 (CH Benzyl), 135.7 (C Benzyl), 136.3 (C Phenyl), 136.8 (4C Indole), 137.4 (C Benzimidazole), 138.0 (C Benzyl), 138.6 (C Phenyl), 142.4 (C Benzimidazole), 152.9 (C Benzimidazole). HRMS (FAB+) *m/z* observed: 772.3309; C54H40N6 [M]+ Required: 772.3314.

1-{3-[Bis(1-methyl-1*H*-indol-3-yl)methyl]benzyl}-2-{3-[bis(1-methyl-1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole (15f). Yellow powder (0.6872 g, 83%). mp 196-198 °C. IR (Solid, ATR, vmax, cm^{-1}) 3050 (w), 2918 (s), 2850 (m), 1731 (w), 1598 (w), 1467 (m), 1268 (m), 1237 (s), 1211 (s), 1062 (m), 984 (m), 807 (m), 738 (s), 578 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.03 (12H, d, 4CH_3 Methyl), 5.30 (2H, s, 2CH Methine), 6.50 (2H, s, CH_2 Methylene), 6.74 (4H, s, 4CH Indole), 6.83 (4H, t, $^3J_{HH}$ 6 Hz 4CH Indole), 7.07-7.23 (6H, m, 3CH Benzyl, 2CH Benzimidazole, CH Phenyl), 7.26-7.35 (6H, m, 4CH Indole, CH Benzyl, CH Phenyl), 7.48-7.57 (6H, m, 4CH Indole, 2CH Benzimidazole), 7.65 (1H, d, $^3J_{HH}$ 9 Hz CH Benzyl), 7.76 (4H, s, 4CH Indole), 8.27 (1H, d, $^3J_{HH}$ 6 Hz CH Phenyl). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 32.9 (Methyl), 41.1 (CH_2, Methylene), 51.8 (CH, Methine), 109.2 (4CH Indole), 112.8 (4C Indole), 118.7 (4CH Indole), 119.0 (CH Benzimidazole), 119.3 (CH Benzimidazole), 119.6 (4CH Indole), 121.5 (CH Indole), 122.9 (CH Benzimidazole), 124.2 (CH Benzimidazole), 126.5 (CH Phenyl), 126.5 (CH Benzyl, 127.4 (CH Benzyl), 128.4 (4CH Indole), 129.2 (4C Indole), 129.6 (CH Benzyl, 130.5 (CH Phenyl), 130.9 (CH Phenyl), 136.2 (CH Phenyl), 136.5 (CH Benzyl), 137.4 (CH Benzyl), 137.7 (CH Phenyl), 138.0 (4C Indole), 138.5 (C Phenyl), 142.3 (C Benzimidazole), 153.3 (C Benzimidazole); HRMS (FAB+) m/z observed: 828.3932; C58H46N6 [M]+ Required: 828.3940.

1-{3-[Bis(2-methyl-1*H*-indol-3-yl)methyl]benzyl}-2-{3-[bis(2-methyl-1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole (15g). Pale orange powder (0.7369 g, 89%). mp 203-205 °C. IR (Solid, ATR, vmax, cm^{-1}) 3483 (br), 3425 (br), 2918 (s), 2850 (m), 1559 (w), 1466 (w), 1248 (s), 1210 (s), 1031 (m), 984 (m), 803 (s), 580 (s). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.09 (12H, s, $4CH_3$), 4.67 (2H, s, 2CH Methine), 6.05 (2H, s, CH2 Methylene), 6.79-6.84 (8H, m, 8CH Indole), 6.87-6.94 (10H, m, 3CH Benzyl, CH Phenyl, 2CH Benzimidazole, 4CH Indole), 7.17-7.25 (8H, m, CH Benzyl, CH Phenyl, 4CH Indole, 2CH Benzimidazole), 7.51 (1H, s, CH Phenyl), 7.74 (1H, d, $^3J_{HH}$ 9 HZ, CH Phenyl), 10-64 (2H, s, 2NH), 10.83 (2H, s, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.6 ($4CH_3$ Methyl), 42.4 (CH Methine), 51.5 (CH_2 Methylene), 111.0 (4CH Indole), 112.4 (4C Indole), 118.5 (4CH Indole), 119.2 (CH Benzimidazole), 119.6 (CH Benzimidazole), 119.9 (4CH Indole), 121.6 (4CH Indole), 123.1 (2CH Benzimidazole), 124.1 (CH Benzyl), 126.6 (CH Phenyl), 127.3 (CH, Benzyl), 128.6 (4C, Indole), 129.2 (CH Phenyl), 129.8 (CH Phenyl), 130.6 (CH Phenyl), 130.9 (CH Phenyl), 131.7 (CH Benzyl), 136.2 (4C Indole), 136.3 (4C Indole), 137.8 (C Benzimidazole), 138.3 (C Benzyl), 138.6 (C Phenyl), 141.6 (C Benzimidazole), 153.1 (C Benzimidazole); HRMS (FAB+) m/z observed: 828.3934; C58H46N6 [M]+ Required: 828.3940.

1-{3-[Bis(2-phenyl-1*H*-indol-3-yl)methyl]benzyl}-2-{3-[bis(2-phenyl-1*H*-indol-3-yl)methyl]phenyl}-1*H*-benzimidazole (15h). Pale yellow powder (0.8963 g, 83%). mp 189 °C. IR (Solid, ATR, vmax, cm^{-1}) 3429 (s), 3351 (br), 3058 (s), 2977 (s), 1622 (s), 1598 (s), 1502 (s), 1455 (s), 1212 (m), 1177 (m), 744 (s). ^{1}H NMR (300 MHz, DMSO-d_6, 300 MHz): δ_H 5.74 (2H, s, 2CH, Methine), 6.08 (2H, s, CH_2, Methylene), 6.70-6.73 (4H, d, $^3J_{HH}$ 9 Hz, 4CH Indole), 6.89 (4H, d, $^3J_{HH}$ 9 Hz, 4CH Indole), 6.95-7.04 (6H, m, 3CH Benzyl, 2CH Benzimidazole, CH Phenyl), 7.06-7.37 (22H, m, 20CH Phenyl, 2CH Benzimidazole), 7.40-7.43 (8H, m, 8CH Indole), 7.50-7.52 (3H, m, 2CH Benzyl, CH Phenyl), 7.80 (1H, d, $^3J_{HH}$ 9 Hz, CH Phenyl), 11.28 (2H, s, 2NH), 11.45 (s, 2H, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 41.0 (CH, Methine), 50.5 ($CH_{2,}$ Methylene), 108.5 (4C Indole), 111.1 (4CH Indole), 118.5 (4CH Indole), 119.3 (CH Benzimidazole), 119.5 (CH Benzimidazole), 120.2 (4CH Indole), 120.4 (4CH Indole), 121.4 (CH Benzimidazole), 123.4 (CH Benzimidazole), 123.8 (4C Indole), 125.2 (CH Phenyl), 128.4 (CH Benzyl), 128.5 (CH Benzyl), 128.5 (4CH Phenyl), 128.7 (4C Indole), 129.0 (4CH Phenyl), 129.1 (CH Benzyl), 129.9 (CH Phenyl), 130.2 (CH Phenyl), 133.2 (CH Benzyl), 136.2 (4C Phenyl), 136.5 (C Benzyl, CH Benzimidazole), 137.4 (C Phenyl), 137.9 (4C Indole), 138.0 (C Phenyl), 142.6 (C Benzimidazole), 153.1 (C Benzimidazole); HRMS (FAB+) *m*/z observed: 1076.4571; C78H56N6 [M]+ Required: 1076.4566.

Acknowledgments

José G. Penieres-Carrillo and Ricardo A. Luna-Mora acknowledge to DGAPA-UNAM the financial support to PAPIIT IN218312 and FES Cuautitlán PIAPI1802 projects. Ricardo A. Luna-Mora acknowledges to CONACYT for Grant 255252.

Supplementary Material

Structure of synthesized IR, MS, ^{1}H NMR, ^{13}C NMR Spectra for synthesized compounds **15a**-**h** can be found in the Online version of the text.

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