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Review

Morita–Baylis–Hillman adducts: Biological activities and potentialities to the discovery of new cheaper drugs

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ABSTRACT

This review aims to present by the first time the Morita–Baylis–Hillman adducts (MBHA) as a new class of bioactive compounds and highlight its potentialities to the discovery of new cheaper and efficient drugs. Now, most these compounds can be prepared fast and on a single synthetic step (one-pot reaction) in high yields and using ecofriendly synthetic protocols. We highlight here the aromatic MBHA, which have shown diverse biological activities as anti-*Leishmania chagasi* and *Leishmania amazonensis* (parasites that cause cutaneous and visceral leishmaniasis), anti-*Trypanosoma cruzi* (parasite that cause Chagas disease), anti-*Plasmodium falciparum* and *Plasmodium berghei* (parasites that cause malaria), lethal against *Biomphalaria glabrata* (the snail transmitter of schistosomiasis), antibacterial, antifungal, herbicide and actives against some human tumor cell lines. Understanding of the biological mechanisms of action of this new class of molecules is still in the infancy stage. However, we report here which has been described to date on the possibilities of biological mechanisms of action, and we present new analyzes based on literature in this area. The academic and industrial interest in selecting *green* and cheaper experiments to the drugs development has been the prime mover of the growth on the subject.

Contents

1. Introduction

The Morita–Baylis–Hillman reaction (MBHR) is a relatively recent form to the C–C bond formation.[1,2] This reaction occurs between an sp^2 electrophilic carbon (e.g., aldehydes, ketones or imines) and the α position of an alkene (or alkyne) connected to an electron-attractors groups (EAG), under tertiary amines as nucleophilic catalysis, being 1,4-diazabicyclo [2.2.2]octane (DABCO) widely used catalyst (Scheme 1).[3] This reaction generates compounds called Morita–Baylis–Hillman adducts (MBHA). The MBHA have been widely used as the starting material in the natural and unnatural products synthesis.[4] When the group X is N (typically NTs) this reaction is classified as Aza-MBHR and products of this reaction are the Aza-MBHA.[4]

This reaction has important features such as the complete atom economy, the possibility of being performed in an aqueous medium or in absence of solvents and on free-metal condition (organocatalysis). These characteristics are today receiving great attention of the synthetic organic chemists which work into academic and industries laboratories on searching on the more ecological, efficient and cheap synthetic protocols to new drug discovery.

A pivotal limitation described in several articles about this reaction is the long reaction time, for example, there are reactions that

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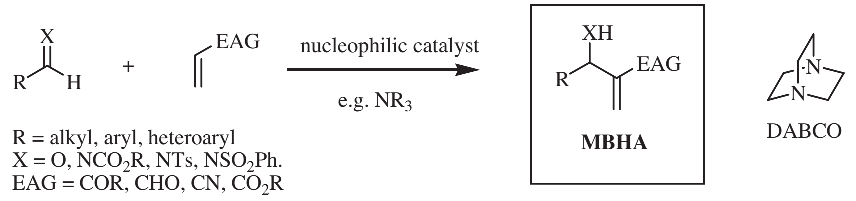


Scheme 1. The Morita–Baylis–Hillman reaction.

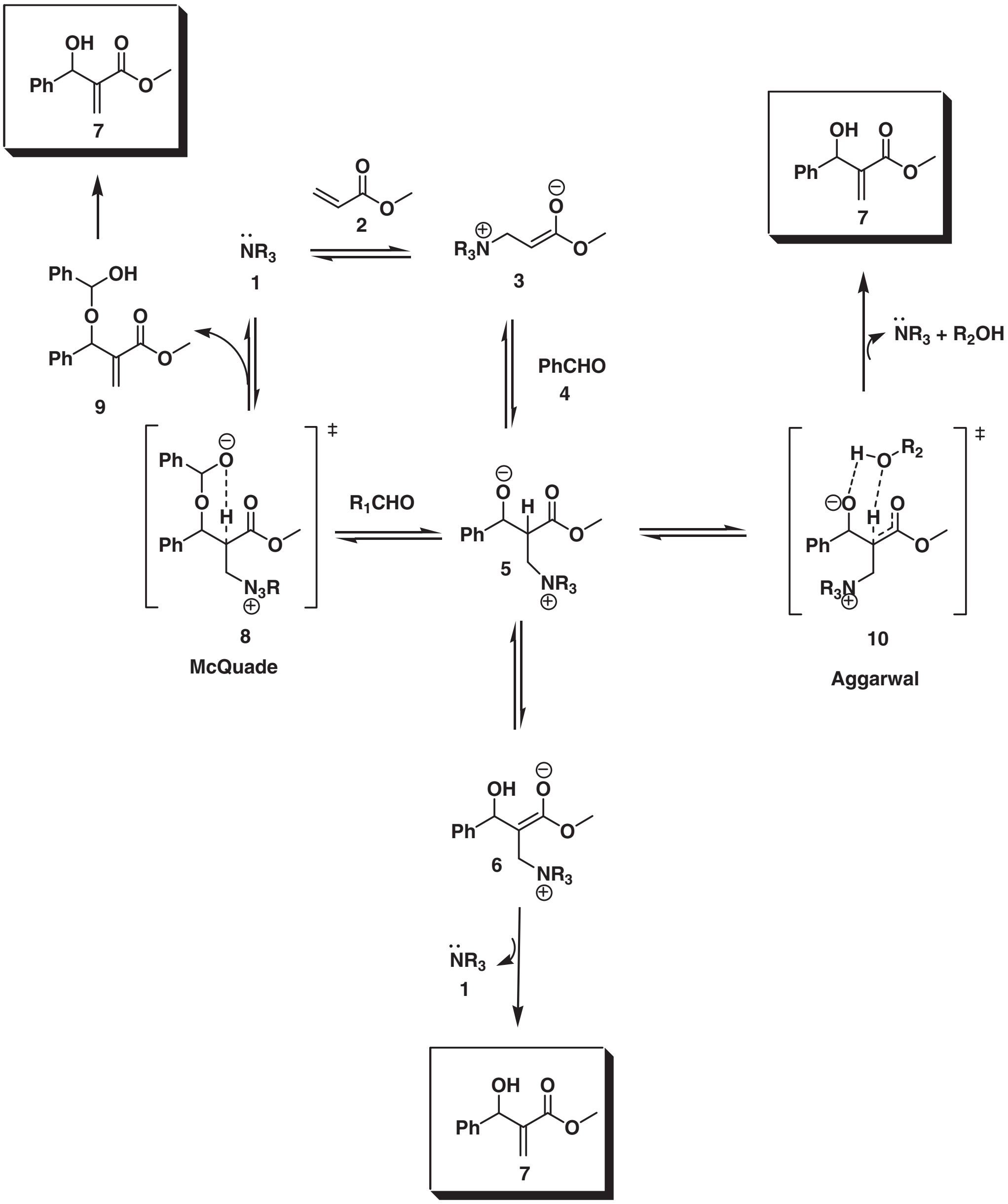
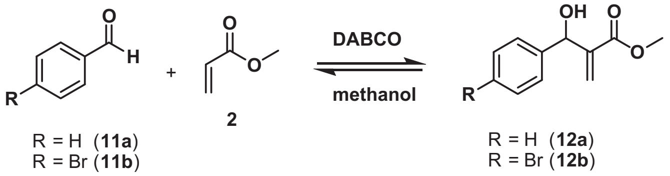


Figure 1. Mechanistic proposals to the MBHR.

were performed in more than 65 days.[3] However, due to the synthetic utility of these MBHA adducts, several protocols have been described an improvement in reaction time and yields, such as the use of ultrasound, high pressures, use of ionic liquids, change of catalyst, change of solvents, microwaves irradiation, and several other experimental protocols.[4]

2. Mechanistic aspects

The first mechanistic proposal for the MBHR was published by Hoffman and Rabe in 1983 following 7 years after by Hill and Isaacs. In these propositions the first step is a Michael addition of the catalyst (tertiary amine **1**) to an activated alkene **2**, generating



Scheme 2. Reversibility into the MBHA.

a zwitterionic enolate **3** (Fig. 1). The next stage consists of an aldol addition of the aldehydes **4** and the intermediate **3** generating the new intermediate **5**, which was proposed as the low step. The subsequent step involves an intramolecular prototropic modification of **5** to **6** that generates the final MBHA **7** after removal of a catalyst that returns to the catalytic cycle. In 2005, McQuade and co-workers and Aggarwal and co-workers, researchers that work in different laboratories, reinvestigated the MBHR mechanism using kinetic and theoretical studies. Differently of previous studies they proposed the proton transfer as the slow step.[5,6] According to McQuade and co-workers, MBHR is a second order kinetic with respect to the aldehydes and they proposed an intramolecular proton transfer as slow step through a six members **8** transition state, generating the intermediate **9**, which becomes the MBHA **7**.[5] Differently Aggarwal and co-workers proposed that in the presence of a proton source, there is a transition state **10** as slow step where the solvent acts as a carrier of the proton from carbon to oxygen

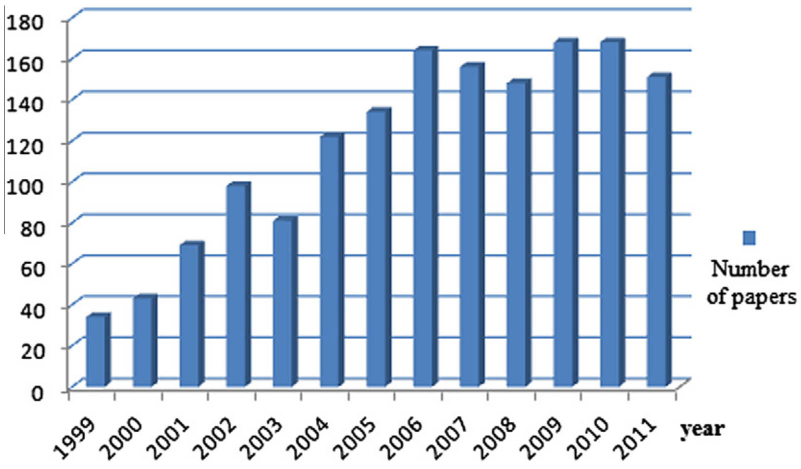


Figure 2. The number of papers published since the 1999th year (until December, 2011) in the keyword 'Baylis' and 'Hillman' (www.scopus.com).

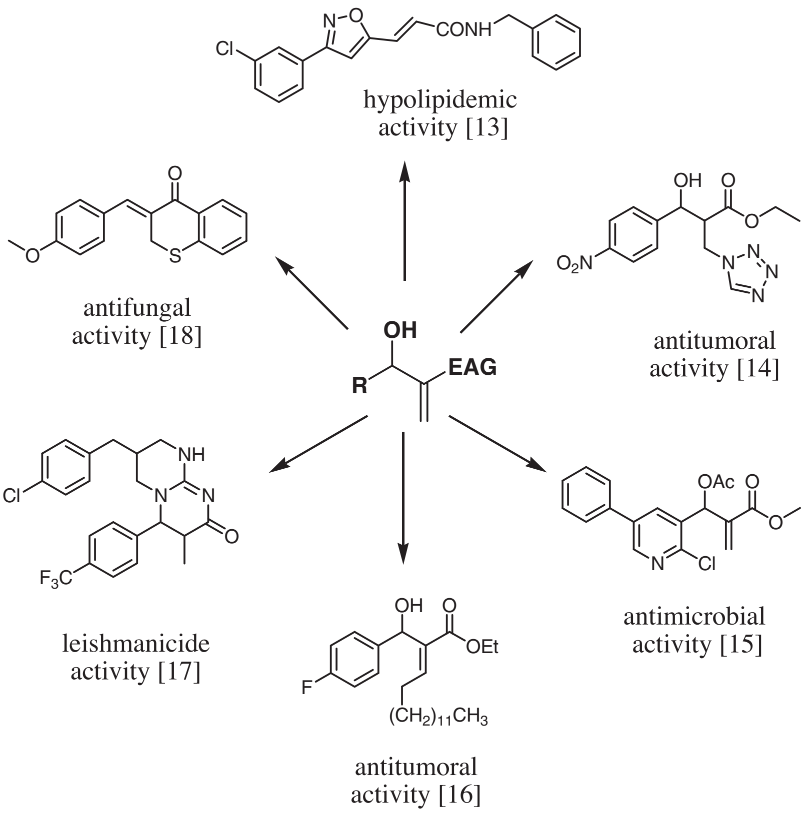


Figure 3. Some example of compounds prepared from MBHA and its biological activities [**13–18**].

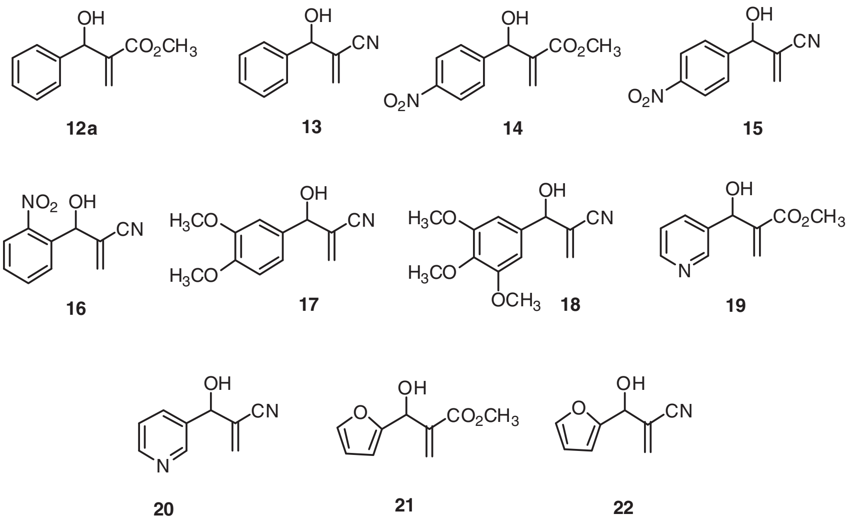
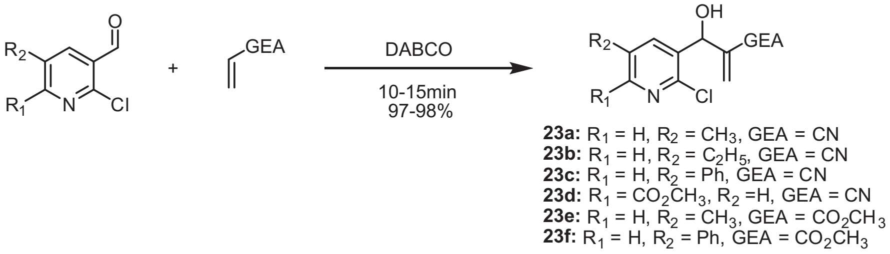


Figure 4. Simple Morita–Baylis–Hillman adduct bio-evaluated by Kundu et al.[19]



Scheme 3. Synthesized and bio-evaluated MBHA by Narender (see Table 1).

(Fig. 1). Coelho and Ebelin intercepted and characterized some of the new intermediaries proposed by McQuade and co-workers and Aggarwal and co-workers using electrospray ionization tandem mass spectrometry (ESI-MS/MS) demonstrating the dualistic nature of the MBHR mechanism.[7] More recently, a computational and experimental investigation of thermodynamic properties and the mechanism of MBHA were performed by Cantillo and Kappe.[8] The authors initially showed that the reaction between benzaldehyde **11a** and methyl acrylate **2** was reversible at 120 °C (Scheme 2), which demonstrates the dependence of the temperature on the equilibrium of reaction. In addition, these researchers amplified the mechanistic knowledge of this reaction suggesting that the slow step of reaction can change depending on the reaction conditions presenting in a unified mechanistic point of view.

Table 1
The MBHA **23a–f** bio-evaluated against strains sensitive and resistant to chloroquine (FLD-B and FLD-NG)

Entry	MBHA	IC_{50} (μg/mL) FLD-B		IC_{50} (μg/mL) FLD-NG	
		SMI	PGI	SMI	PGI
1	**23**°	1.25	1.3	22.5	10.5
2	**23b**	1.8	4	2.5	5.5
3	**23c**	3.6	8	0.9	2.2
4	**23d**	3.4	7	5.75	6.75
5	**23e**	18	28.5	3.05	5.75
6	**23f**	45	115	5	10.75
7	Chloroquine	0.004	0.005	–	–

SMI = schizont maturation inhibition; PGI = total parasite growth inhibition.

Very recently Vasconcellos's research group described the reversibility for the reaction between *p*-bromobenzaldehyde 11b and methyl acrylate **2**.[9] In their study, **12b** could be prepared in a very high yield at 0 °C. When pure **12b** reacted under microwave irradiation at 120 °C for 10 min, methyl acrylate and *p*-bromobenzaldehyde were obtained. Interestingly, the product **12b** was not formed when the reaction mixture was left under microwave irradiation at 80 °C, confirming that this reaction can be endergonic at higher temperatures (Scheme 2).

3. The growth and the present status

The last general review about MBHR was recently published by Basavaiah et al. in 2010 where the 1028 references cited therein shows the importance of this reaction for synthetic organic chemistry, in addition to the progress on the search for new asymmetric catalysts, intramolecular version, heterocyclic synthesis and advances in mechanistic understanding.[4] A recent book published last year by Shi et al. entitled 'The Chemistry of the Morita–Baylis–Hillman Reaction' also demonstrates the great interest of the scientific community about this reaction, both graduated and undergraduate students and all chemists working in academic and industrial laboratories. This book has 705 pages where it tells not only the historical aspects related to the reaction as well as synthetic applications, reaction mechanism, and use of asymmetric version MBHA and derivatives in the construction of heterocyclic and natural products.[10] The impressive growth in the number of papers published about MBH chemistry can be observed in the SCOPUS database (Fig. 2) that shows the number of published scientific articles from 1999 until December 2011.

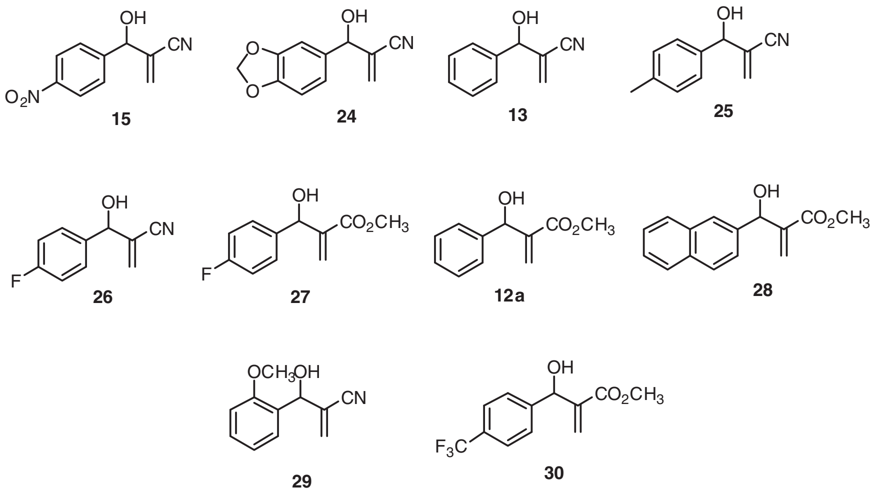


Figure 5. The bio-evaluated MBHA against *Biomphalaria glabrata*.

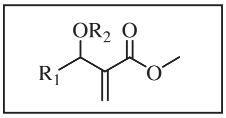
4. The Morita–Baylis–Hillman adducts

4.1. The use of MBHA as starting material on the chemical synthesis

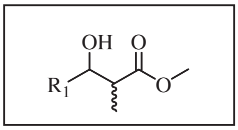
Since the work of Drewes and Emslie[11] and Hoffman and Rabe,[12] the MBHA have been used by chemists as synthetic intermediates on total synthesis. Various natural products and molecules of biological interest were synthesized from MBHA or using the MBH reaction as the key step for the preparation of compounds with biological interest.[4] For example, in Figure 3 below we show some compounds prepared from MBHA and its biological activities.[13–18] However, it is important to detach here that the use of MBHA for synthesis of more complex bioactive compounds is not the objective of this review. As already commented in this paper, for this, other very large reviews[3,4] and book[10] some has recently been published.

4.2. Biological evaluations of simples MBHA

The simple MBHA bioevaluation prepared from aromatic aldehydes and activated alkenes was explored only three decades after the publication of the Morita work.[1] The first report of biological



31:R_1 = ethyl; R_2 = H
32:R_1 = propyl; R_2 = H
33:R_1 =2-thiophenyl; R_2 = H
34:R_1 =3-pyridinyl; R_2 = H
35:R_1 =3-quinolinyll; R_2 = H
14:R_1 = *p*-nitrophenyl; R_2 = H
36:R_1 = *p*-chlorophenyl; R_2 = H
37:R_1 = *p*-trifluoromethyl; R_2 = H
38:R_1 = *p*-cyanophenyl; R_2 = H
39:R_1 =*p*-trifluoromethoxyphenyl; R_2 = H
40:R_1 =*p*-methylsulphonylphenyl; R_2 = H
41:R_1 =*p*-methoxyphenyl; R_2 = H
42:R_1 =3,4-methylenedioxyphenyl; R_2 = H
43:R_1 = *p*-hydroxy-*m*-methoxyphenyl; R_2 = H
44:R_1 = *p*-(N,N-dimethyl)aninophenyl; R_2 = H
45:R_1 = 3,4,5-trimethoxyphenyl; R_2 = H
46:R_1 = *p*-nitrophenyl; R_2 = TBS
47:R_1 = *p*-trifluoromethyl; R_2 = TBS
48:R_1 = *p*-cyanophenyl; R_2 = TBS
49:R_1 = *p*-trifluoromethoxyphenyl; R_2 = TBS



50:R_1 = *p*-nitrophenyl
51:R_1 = *p*-trifluoromethyl
52:R_1 = *p*-cyanophenyl
53:R_1 = *p*-trifluoromethoxypheny

Figure 6. MBHA and derivatives bio-evaluated by Almeida and co-workers.[22]

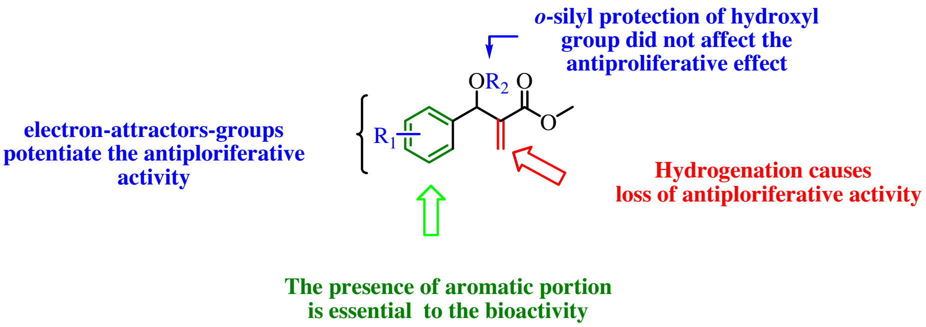
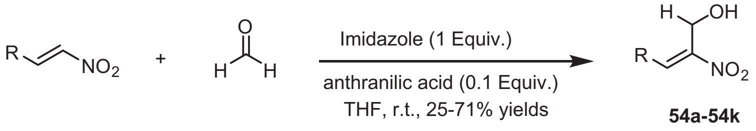


Figure 7. The SAR analysis of the 18 MBHA bio-evaluated on cell lines (e.g., NCIADR).[22]



Scheme 4. Conjugated nitro alkenes and formaldehyde as staring material to MBHA **54a**–**54k** preparations (see Table 2).

activity of MBHA dates from 1999, when Kundu et al.[19] reported a significant antimalarial activity of eleven simple MBHA against in vitro *P. falciparum* and *P. berghei* (Fig. 4). The adducts **15** and **20** demonstrated greater potency against *P. berghei* at a dose of 80 mg/kg.

In 2005, Narender et al. synthesized in excellent yields (97–98%) six adducts using *o*-chloronicotinaldehydes and acrylonitrile or methyl acrylate as starting material (Scheme 3).[20] The bio-evaluation against strains sensitive and resistant to chloroquine (FLD-B and FLD-NG) showed significant antimalarial activity for all compounds synthesized. The MBHA **23a**, **23b** and **23c** are the most active in both strains (Table 1). In this same paper, they presented the first structure–activity relationship (SAR) to this new class of bioactive compounds that showed the nitrile groups and the phenyl group on the R_2 position important for the antimalarial activities of (Table 1, entries 1–4).[20]

In 2006, Vasconcellos et al. reported the activity of aromatic Morita–Baylis–Hillman adducts against *Biomphalaria glabrata*, a snail which is the secondary schistosomiasis vector.[21] The Figure 5 shows the synthesized and bio-evaluated MBHA in this work. The MBHA **15**, **24** and **28** were those that showed higher molluscicidal activity with LC_{50} of 7.50 µg/mL, 6.64 µg/mL and 1.17 µg/mL, respectively. Then, the importance of the presence of the nitro group attached to the aromatic ring to a significant molluscicidal activity and the presence of the nitrile group was observed. Besides that, the β-naphthyl and 3,4-methylenedioxyphenyl groups, which are bioisosteres each other, are also responsible for high molluscicidal activity of this class of compounds.

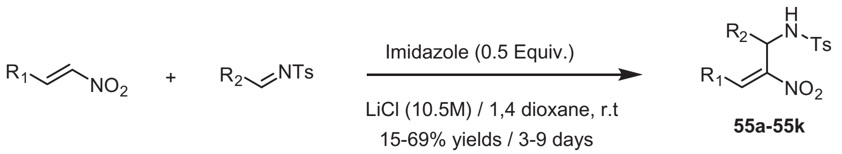
That same year, Almeida's research group performed the synthesis of eighteen aromatic and aliphatic MBHA (Fig. 6) and also some derivatives from MBHA. They described in vitro antiproliferative activities against eight cancer cell lines human tumor cell line type (UACC62, MCF7, NCIADR, 786-0, NCI460, PC-03, OVCAR, HT29 and NCIADR).[22]

A SAR study showed very relevant information (Fig. 7), such as the importance of the α,β-unsaturated double bond and the electron-attractor groups linked to the aromatic ring for the optimization of the antitumor activity. The hydrogenated derivatives (**50**–**53**, Fig. 6) of the most active studied compounds were tested. Neither of them inhibited cell proliferation at any concentration. Besides this, O-silylprotection of hydroxyl group (derivatives **46**–**49**) did not affect the antiproliferative effect on the most cell lines in a significant way. Another very important observation highlighted in Almeida's article was that the aromatic compounds were significantly more active than non-aromatic ones. These results support the previous and all subsequently studies in this area, where only aromatic (or heteroaromatic) MBHA have been synthesized and bio-evaluated. In fact, it is already known that aromatic and/or heteroaromatic rings are ubiquitous features in small-molecule drugs.[23] The fewer the number of aromatic and/or heteroaromatic rings contained in a drug candidate, the more developable that candidate is likely to be; specifically, more than three aromatic rings in a molecule correlates with poorer compound developability and, therefore, an increased risk of compound attrition.[23]

Shortly after Namboothiri's research group published three articles reporting the bioactivities of several MBHA as anticancer. They were obtained using the conjugated nitroalkenes aromatic as Michael acceptor catalyzed by imidazole. In their first article,[24] 11 MBHA were obtained by reaction between nitroalkenes as Michael acceptor with formaldehyde using anthranilic acid as an additive (Scheme 4). The adducts were synthesized in low to moderate yields (25–71%) and testing on the cervical cancer cells (HeLa) and demonstrated that the adducts **54b**, **54e** and **54g** showed IC_{50} of 2 µM, 2 µM and 3 µM, respectively (Table 2, entries 2, 5 and 7). Studies on the biological mechanism of action showed that these MBHA inhibited the tubulin formation that promotes cellular microtubule depolymerization.[24]

Table 2
Yields and bioactivities of the MBHA **54a**–**54k** in cervical cancer cells (HeLa)

Entry	MBHA	R	IC_{50} (µM)
1	**54a**	2-Furyl	22
2	**54b**	2-Thienyl	2
3	**54c**	3-Furyl	5
4	**54d**	3-Thienyl	5
5	**54e**	*p*-OMePh	2
6	**54f**	*o*-NO_2Ph	>50
7	**54g**	*m*,*p*-$(OMe)_2$Ph	3
8	**54h**	*m*-OMe-*p*-OH-Ph	NI
9	**54i**	*m*,*p*(OCH_2O)Ph	38
10	**54j**	*p*-F-Ph	NI
11	**54k**	Ph	40



Scheme 5. Conjugated nitro alkenes and *N*-tosylimines as staring material to MBHA **55a**–**55k** preparations (see Table 3).

Table 3
Yields and bioactivities of the MBHA **55a**–**55k** in cervical cancer cells (HeLa)

Entry	MBHA	R_1	R_2	IG (%) (5 μM)
1	**55a**	2-Furyl	Ph	44
2	**55b**	2-Furyl	4-OMePh	25
3	**55c**	2-Furyl	2-Furyl	32
4	**55d**	3-Furyl	Ph	28
5	**55e**	3-Furyl	2-Furyl	33
6	**55f**	2-Thienyl	Ph	49
7	**55g**	2-Thienyl	2-Furyl	28
8	**55h**	3-Thienyl	Ph	45
9	**55i**	*p*-OMePh	Ph	23
10	**55j**	*m*,*p*-$(OMe)_2$Ph	Ph	35
11	**55k**	*m*,*p*(OCH_2O)Ph	Ph	29

IG—inhibition growth.

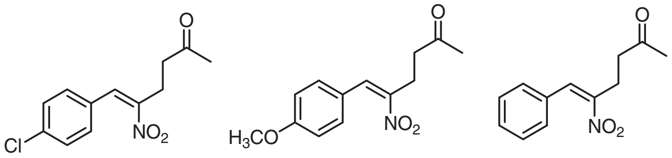

56a **56b** **56c**

Figure 8. More active adducts against HeLa with inhibition above 70% at a concentration of 5 μM. We included these results in this review by that compounds have been considered by the authors as MBHA.

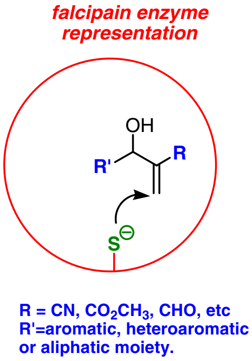


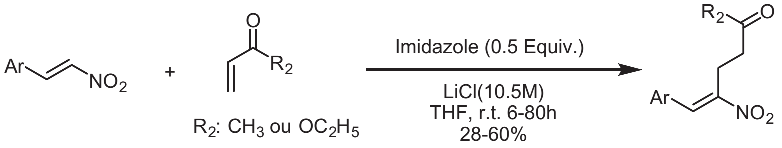
Figure 9. Representation of an inactivation of enzyme falcipain.

In their second paper[25] Namboothiri and co-workers synthesized eleven adducts using *N*-tosylimines as electrophilic (an Aza-MBHR) substrate, LiCl as an additive using 1,4-dioxane as solvent (Scheme 5 and Table 3). The Aza-MBHA **55a**–**55k** were synthesized and incubated with cervical human cancer cells (HeLa) at of 1 μM, 5 μM and 10 μM concentrations for 24 h, where the compounds **55a**, 55f and **55h** showed in vitro cells (HeLa) inhibition > 40% to 5 μM (Table 3, entries 1, 6 and 8). These Aza-MBHA also inhibited in vitro the tubulin formation that causes cellular microtubule depolymerization similar as observed in their first article.[24]

Next, Namboothiri and co-workers reported the synthesis of 14 MBHA now using aromatic nitroalkenes with ethyl acrylate or methyl vinyl ketone as electrophiles under imidazole as catalyst,[26] as shown in Scheme 6. The adducts **56a**, 56b and **56c** were those who also showed better activity against human cervical cancer cells (HeLa) with inhibition of growth of these cells above 70% at a concentration of 5 μM (Fig. 8). The adduct **56b** proved to be the most potent with 80% inhibition at a concentration of 5 μM and all adducts showed affinity for tubulin.

At this point some considerations on possible biological mechanisms of action of these compounds as antimalaria and anticancer are appropriate. Bioligands presenting α,β-unsaturated moieties are electrophiles and can react with SH, NH and OH groups (nucleophilic groups) present in receptors or enzymes. As presented here, in particular, some MBHA have demonstrated important bioactivity against *P. falciparum* (malaria).[19,20] It may be suggested that inactivation of falcipain enzyme (essential for the life cycle of *P. falciparum*) takes place through of an irreversible nucleophilic addition of thiol group present in the cysteine proteases on the conjugated double bond (Fig. 9).[27]

Moreover, β-hydroxyacrylates have been investigated toward biological nucleophiles, with evidence of significant interaction with glutathione rather than with deoxyribonucleosides.[28]On the Rauth and co-workers' studies[28] that cellular redox state as mediated by protein-sulphydryl status is a major alternative to DNA as a target for the effects of reduction products of 2-nitroimidazoles.[28]It is already well known that compounds that either inhibit or stimulate GSH synthesis or affect its intracellular concentration may then be of value in cancer chemotherapy[29,30] due cellular glutathione (GSH) levels were found to be higher in human cancer cell lines than in a normal cell.[31,32] There are evidences showing that agents altering GSH concentration affect transcription of detoxification enzymes, cell proliferation, and apoptosis.[33] In 2007, Goulart and Almeida's research groups described an electrochemical study with MBHA **14**.[34] They observed formation of a transient nitroso species of MBHA like-14 in presence of GSH, considering **14** as a bioreductive agent with a function of decreasing levels glutathione (Fig. 10).[30] Based on these two previous explanations we can classify the nitro groups and the conjugated double bonds in the MBHA as possible pharmacophoric groups.



Scheme 6. Obtained adducts by reaction of substituted nitroalkenes and ethyl acrylate or methyl vinyl ketone (14 similarly adducts, not showed here).

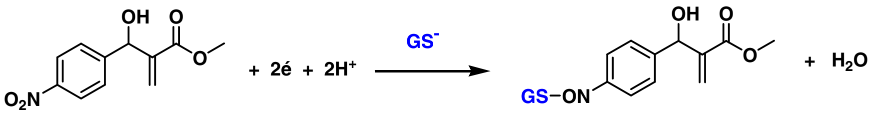


Figure 10. Adduct formation between reduced **14** and GS$^-$.[34]

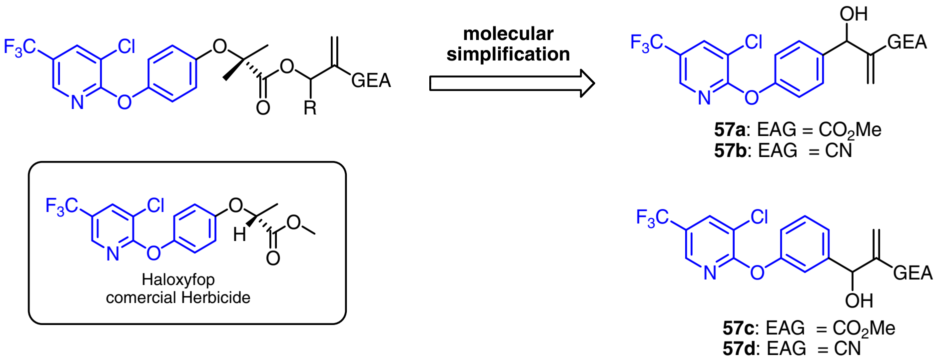


Figure 11. Some MBHA presenting herbicidal and antifungal bioactivities.

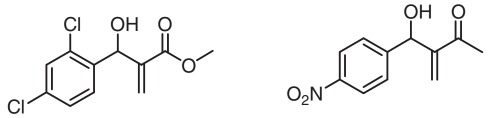


Figure 12a. The MBHA 2-[(2,4-dichlorophenyl)(hydroxy)]methylacrylate (**58**) and 3-[hydroxy(4-nitrophenyl)methyl]but-3-en-2-one (**59**) as herbicides.

In sequence, Xu' research group also reported in 2006 the herbicidal and antifungal activities of a few 3-chloro-5-(trifluoromethyl)-pyridin-2-il-oxy)phenyl derivatives containing acrylonitrile and acrylates moieties into the structures.[35] The design of these new MBHA was based on the structure of Haloxyfop® (Fig. 11), a commercial herbicide. Through molecular simplification strategy, fifteen compounds were synthesized, where the **57a** and **57c** adducts showed a pronounced fungicidal activity controlling 80% and 70% of the mildew on cucumbers 400 g ai/ha. The adduct **57b** was effective against rice blast with 85% of control at 25 g ai/ha. In this study, we also observed the loss of fungicidal activity after the etherification of the hydroxyl group of synthesized MBHA, which demonstrates the importance of this functional group.

The herbicidal activity of some MBHA were also described very recently by Yang' research group.[36] They published the synthesis of nineteen MBHA at room temperature using trimethylamine or DABCO as catalyst and showed that 2-[(2,4-dichlorophenyl)(hydroxy)]methylacrylate (**58**) exhibited broad-spectrum herbicidal activity, with 100% control of broad-leaved weeds *Zinnia elegans* Jacq. and *Abutilon theophrasti*, 80% and 75% control of grass weeds *Echinochloa crusgalli* Baeuv and *Digitaria sanguinalis* Scop at 2000 g ai/ha, respectively. Moreover, 3-[hydroxy(4-nitrophenyl)methyl]but-3-en-2-one (**59**) exhibited efficient fungicidal activity, with 100% control of *Phytophthora infestans*, 50% and 50% control of *Sclerophtho-ramacrospora* thirumctal (RB) and *Bocrytis cinerea* Pers at 25 g ai/ha (Fig. 12a).[36]

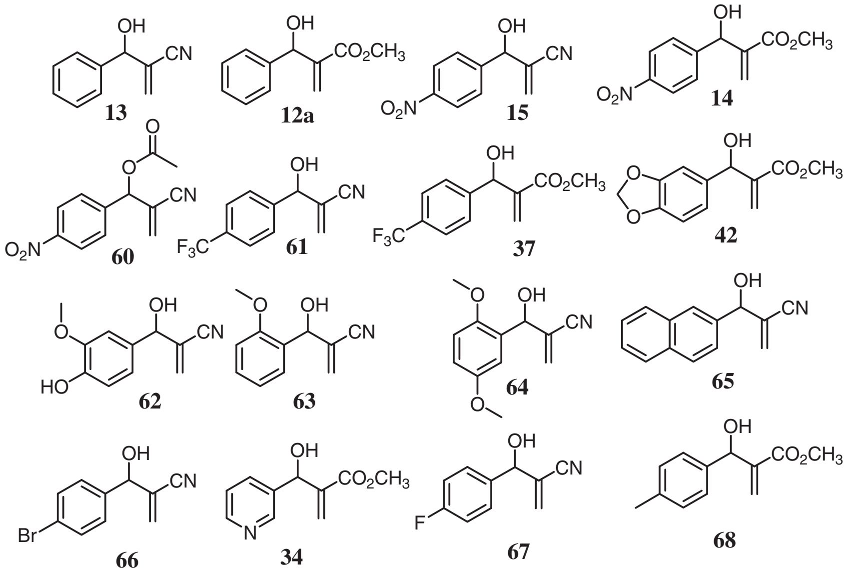


Figure 12b. First MBHAs evaluated against promastigote and amastigote forms of *Leishmania amazonensis*.

Table 4
Antileishmanial activity and cytotoxicity against macrophages of 16 MBHA (Figs. 12a and b) and reference drug Pentostam (50 mM)[37]

MBHA	Promastigote inhibition (%)	Amastigote inhibition (%)	(%) Macrophage LDH release	IC_{50} (μM)
13	42.2	48.1	0.0	49.3
12a	37.6	14.4	0.0	-
15	47.0	93.9	41.7	7.9
14	67.3	80.6	41.6	-
60	59.3	21.5	0.0	-
61	62.8	86.0	36.3	-
37	67.6	89.0	36.2	42.8
42	25.5	9.1	0.0	-
62	6.6	19.7	0.0	-
63	30.0	14.7	6.1	-
64	22.3	35.3	0.0	-
65	24.0	95.6	26.6	11.2
66	17.5	84.3	0.0	12.5
34	39.6	8.9	13.2	-
67	32.4	33.6	0.0	-
68	32.4	28.7	0.0	-
Pentostam	0.0	35.3	13.2	47.7

Antiamastigote IC_{50} of selected compounds.

In 2007, Vasconcellos and co-workers presented by the first time the bioactivity of fifteen MBHA against promastigote and amastigote forms of *Leishmania amazonensis* (Fig. 12b),[37] a parasite that causes cutaneous and mucocutaneous leishmaniasis. The adduct **15** was the most active with IC_{50} value of 7.9 μM (Table 4, entry 2). However, studies in macrophages by measuring the levels of enzyme lactate dehydrogenase (LDH) showed that these adduct possessed considerable cytotoxicity. On the other hand, the adduct **60** was considered the most selective of the series presenting a IC_{50} of 12.5 μM and 0.0% of LDH release in macrophages at 50 μM. The tests also showed that none of the 15 synthesized MBHA induced nitric oxide production in culture medium, an important experimental result to discard this type of biological action mechanism.

The preliminary analysis of the structure–activity relationship (SAR) of the aromatic 16 MBHA (Fig. 25, Table 4) revealed that the presence of a high electron-attractor group such as NO_2 in the aromatic moiety significantly increased the antiamastigote activity but also rendered them more toxic to macrophages (**13** and **12a vs 15** and **14**, Table 4). The OH group acetylating in **15** lowers its cytotoxic effects (**15** vs **60**, Table 4) indicating the importance of the alcohol function on the MBHA. Oxygenation of aromatic ring (electron donor groups) seems to decrease the biological activities (see **42**, **62**, **63** and **68**). In general nitrile is more active than esters. Note that the compound **13** is more active than **12a**. Compound **66** was found to be most selective against amastigotes, inhibiting 84.3% of parasite growth concomitant with 0% release of LDH by macrophages at 50 mM. This was likely due to the presence of the bromine atom, not found in the less active **13**. That was less toxic to macrophages than the naphthyl group in compound **65** (26.6% LDH release).

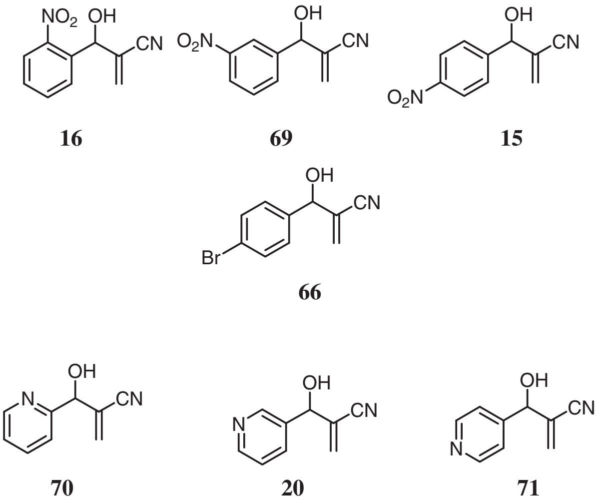


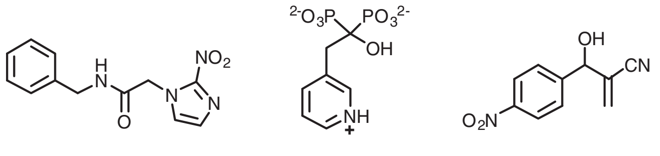
Figure 13. The MBHA bio-evaluated against *Artemia salina* and *Leishmania chagasi*.[38]

Based on this results, Vasconcellos's research group described in 2009 the synthetic optimization of seven MBHA (Fig. 13) and their bioevaluation against *Artemia salina* Leach, and against the promastigote form of *Leishmania chagasi*, the main parasite that causes visceral leishmaniasis, the most lethal form of this neglected disease in Brazil.[38]All adducts showed high leishmanicidal activity with IC_{50} values between 25.2 μM and 38.8 μM (Table 5). The adduct **66** was also the most active among the bioavailability adducts with IC_{50} of 25.2 μM in *L. chagasi* and 129.83 μM in *Artemia salina.* is important to emphasize that the biological evaluations used in the previous articles was not the same. It is observed that the method Elisa/MTT (used in the study published in 2009) is less sensitive than the determination by fluorimetry (used in the study published in 2007). Thus, the absolute values obtained from these two articles should not be compared, and we can only consider the relative values in each article.

In 2010, the Vasconcellos's research group also presented an unprecedented study on the MBHA **15** in relation to the bioactivity against epimastigote and trypomastigote forms of *Trypanosome cruzi.*[39] MBHA **15** showed potent growth inhibition of both epimastigotes and of trypomastigotes, with IC_{50} values of 28.5 μM and 25.5 μM, respectively. In this article ultra structural analysis was performed, showing significant morphological changes in both forms of *T. cruzi* when treated with the adduct **15** (Fig. 14). It could be highlight the increase in volume and rounding of the cell body, intense cellular disorganization and disruption of the nuclear membrane with loss of nuclear material, indicating that different mechanisms of cell death were occurring as apoptosis, necrosis and autophagy.[40] These results led to the proposal more two simultaneous mechanisms of action for this adduct. The morphological changes predominantly found in trypomastigote forms, suggests that compound **15** disturbs the integrity of organelles in at least two distinct mechanisms: The first proposed mechanism is based on the studies carried out by Tonin et al. who have demonstrated that the redox potential of the nitro group has influence on the trypanocidal activity.[41]The main intermediate products responsible for the cytotoxic action of the nitrocompounds are

Table 5
The bioactivity of MBHA against *Artemia salina* and promastigote forms of *Leishmania chagasi*[38]

Entry	MBHA	LC_{50} (μM) *Artemia salina*	IC_{50} (μM) Promastigotes of *L. chagasi*
1	**16**	430.39	38.8
2	**69**	471.07	34.6
3	**15**	180.39	37.4
4	**66**	129.83	25.2
5	**70**	545.00	32.0
6	**20**	555.00	36.9
7	**71**	443.12	30.1



Benznidazole **Risedronate** **15**

Figure 14. Structures used on the molecular docking calculations.

the nitro-radical anion ($NO_2^{\cdot -}$) and hydroxylamine derivative (R-NHOH), which are produced in the reduction of the nitro group similar way to the benznidazole derivatives mechanism.[41]The second proposed mechanism suggests that the **15** may act through the inhibition of the *Tc*FPPS enzyme, which takes part in early catalytic steps of sterols biosynthesis pathway. Specific endogenous sterols have a remarkable part in growth and development of *T. cruzi* and Leishmania parasites because of their participation in post-translational regulation mechanisms, especially prenylation,[42] which means that sterols biosynthesis inhibitors can be very potent anti-parasitic drugs.[43,44] Such data suggests that inhibition of *Tc*FPPS depletes the parasite stocks of these essential endogenous steroids, inducing the parasite cell death throughout apoptosis, autophagy or necrosis[40] which ultimately leads to the morphological changes seen in Figure 15.[39] such as nucleus

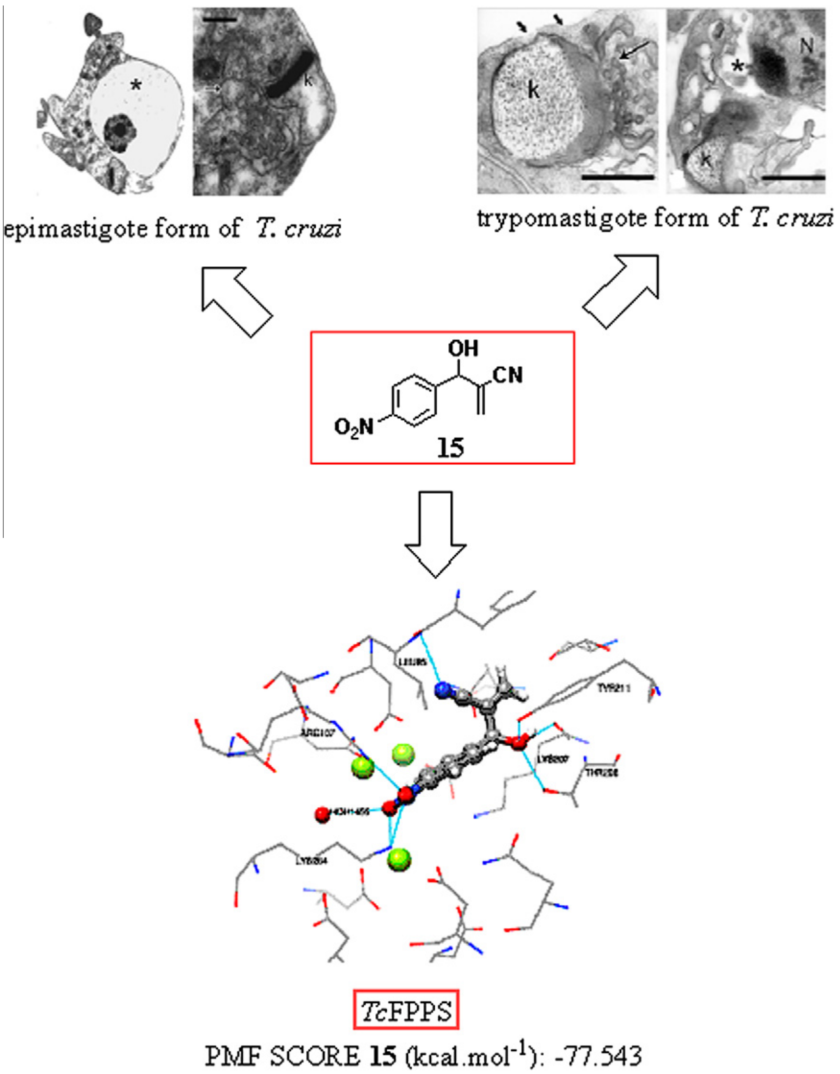
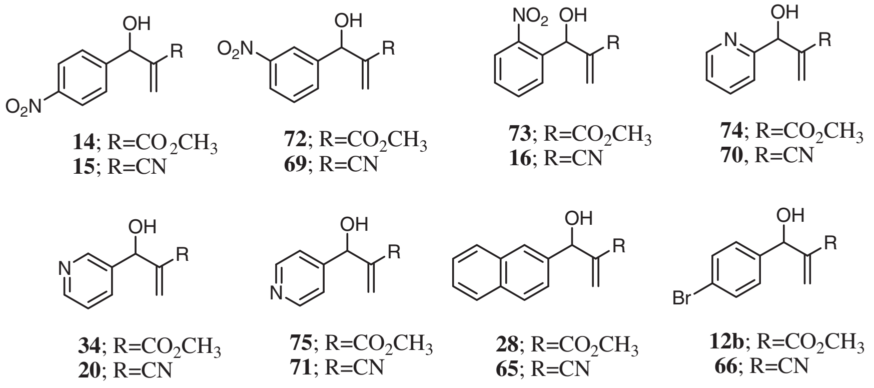


Figure 15. Experimental ultra structural analysis and in silico calculations of MBHA **15**.



14; R=CO_2CH_3
15; R=CN
72; R=CO_2CH_3
69; R=CN
73; R=CO_2CH_3
16; R=CN
74; R=CO_2CH_3
70, R=CN
34; R=CO_2CH_3
20; R=CN
75; R=CO_2CH_3
71; R=CN
28; R=CO_2CH_3
65; R=CN
12b; R=CO_2CH_3
66; R=CN

Figure 16. Sixteen aromatic MBHA analyzed against promastigote forms of *L. amazonensis* and *L. chagasi* by use of MTT/Elisa methodology.

swelling, mitochondrial fragmentation with profound changes in the kinetoplast network and rupture of plasma membrane. Vasconcellos's research group also performed in the same article a molecular docking study with the Risedronate, known inhibitor of this enzyme, the adduct **15**, and also with benznidazole, where it is known that the mechanism of action is not the inhibition of the *Tc*FPPS,[45]used for validation of this theoretical study (Fig. 14). The MBHA15 showed good affinity on *Tc*FPPS in silico (PMF SCORE = −77.543 kcal mol^{-1}). As the Risedronate is more active than MBHA **15** was expected a more negative calculated score value for Risedronate. In fact, the calculated score to Risedronate (PMF SCORE = −119.142 kcal mol^{-1}) was in agreement with the experimental data. As also expected the calculated value of score to Benznidazole was positive, which is in agreement with experimental data due the fact that Benznidazole does not act in *Tc*FPPS. These calculations indicated that *Tc*FPPS can also be a possible biological target of the MBHA **15**.

Aimed at analyzing a larger group of MBHA by the same biological methodology, Vasconcellos's research group published the bioevaluation of sixteen aromatic MBHA (Fig. 16) against promastigote forms of *L. amazonensis* and *L. chagasi* using MTT/Elisa methodology to measure the bioactivity of all compounds together, that proved to be more reliable to be performed the accurate analysis of the structure–activity-relationship (SAR) for this congener series.[46]

All bio-evaluated MBHA showed leishmanicidal activity. Again, MBHA that present the nitrile group as EAG were more bioactive than the MBHA presenting EAG = CO_2CH_3. The authors proposed that the formation of intramolecular hydrogen bond (IHB) between the hydroxyl and carbonyl ester portion could decrease the interaction of these compounds with the active site of a donor or acceptor of hydrogen present in target enzyme. Interestingly, the nitrile **16** possessed activity similar to its analog ester. The authors explained this similar leishmanicidal activity based on the formation of an remarkable seven member IHB between the nitro group located in *o*-position of the aromatic ring, and hydroxyl group ($NO_2\cdots HO$), which is characterized in 2007 by the same research group by calculation using the Quantum Theory Atoms in Molecules (QTAIM, Fig. 17).[47]

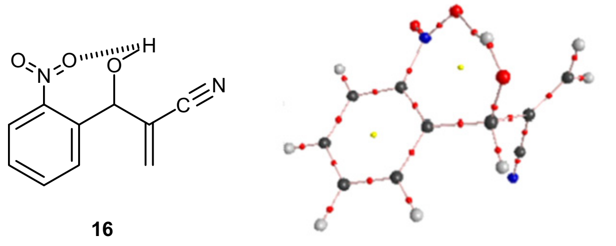


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Figure 17. Characterized seven member IHB $NO_2\cdots HO$ by QTAIM calculations.

In 2011, the Vasconcellos's research group published two articles where two different congener series of new MBHA were designed based on bioisosterism and molecular hybridization, two classical strategies in medicinal chemistry which are useful tools in the design of new drug.[48,49]

The first article reported the synthesis of sixteen MBHA, eight obtained by reaction between aromatic aldehydes and propyl acrylate (MBHA **76**–**83**, Fig. 18) and eight corresponding bioisosters, where the CH_3 group was replaced by the OH group in the series, producing the MBHA **84**–**91**, as shown in Figure 17 and Table 6[50] The modification of the lipophilicity (log*P*) and the number of donors and acceptors of hydrogen bonds of the MBHA was carried out in order to observe the influence of these parameters in the leishmanicidal activities on promastigotes form of *L. amazonensis.* Interestingly no significant change of bioactivity was observed in these 16 MBHA (Table 6) comparing the series **76**–**83** versus series **84**–**91**, probably due to compensation between the increase of lipophilicity and increase of a donor group and an acceptor of hydrogen bonds.

However, some important results could be obtained increasing the understanding of possible biological action mechanisms of these compounds. For example, the MBHA that have nitro group attached to the aromatic ring in *ortho* position were again the most active against the promastigote forms of *L. amazonensis* with IC_{50} values of 28.38 μM and 20.52 μM, respectively (Table 6, entries 1 and 9). In addition, both showed good levels of selectivity index (SI) of 4.75 and 5.43, respectively.

In this article the authors proposed that the formation of IHB as a determining effect in controlling the conformation of the adduct **84**, which could influence the redox potential of these compounds and consequently on their activity against the parasite in the study. It can be seen in Figure 19 that the conformational minimum is calculated to **84** places the nitro group out of the plane on aromatic ring in the same way that the *ortho* substituted compounds previously described in other articles. This geometry could facilitate the potential reduction (more electrons affinity) generating free radicals NO easily, acting in the oxidative stress mechanism. The dihedral angle between the nitro group and aromatic ring was calculated to be 26.89° using HF/6–31+G(d) as level of calculation and implementing the Polarization Continuum Model (PCM) on DMF to simulation of the lipophilicity of the cell membrane.

In the second article published in 2011 by Vasconcellos's research group, the design of the new congener series of MBHA was based on the concept of molecular hybridization (Fig. 20), where the aromatic aldehydes and the unpublished methyl

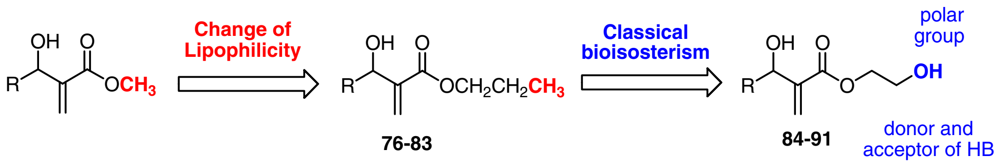


Figure 18. Design based on classic bioisosterism to realize a new congener series of MBHA.

Table 6
Leishmanicide activity and selectivity index of the MBHA **76–91**

Entry	MBHA	R	IC_{50} (μM)	SI
1	**76**	*o*-$(NO_2)C_6H_4$	28.38	4.75
2	**77**	*m*-$(NO_2)C_6H_4$	72.23	1.57
3	**78**	*p*-$(NO_2)C_6H_4$	52.04	2.33
4	**79**	2-C_5H_4N	194.07	3.68
5	**80**	3-C_5H_4N	210.81	1.81
6	**81**	4-C_5H_4N	148.60	1.83
7	**82**	2-$C_{10}H_7$	54.48	2.59
8	**83**	*p*-$(Br)C_6H_4$	74.70	1.67
9	**84**	*o*-$(NO_2)C_6H_4$	20.52	5.43
10	**85**	*m*-$(NO_2)C_6H_4$	64.57	1.06
11	**86**	*p*-$(NO_2)C_6H_4$	53.03	0.88
12	**87**	2-C_5H_4N	266.32	2.81
13	**88**	3-C_5H_4N	323.77	1.29
14	**89**	4-C_5H_4N	381.65	1.20
15	**90**	2-$C_{10}H_7$	52.54	2.24
16	**91**	*p*-$(Br)C_6H_4$	56.73	2.77

SI—selectivity index.

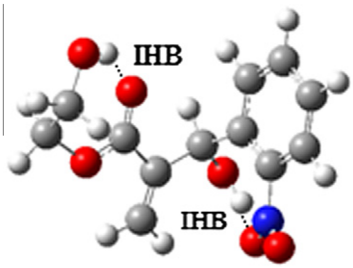


Figure 19. Calculated conformational minimum to MBHA **84**.

acrylate salicylate **92** were efficiently synthesized and reacted under DABCO catalysis, leading the **93a–93f** in good yields.[51] These new MBHA were bio-evaluated against the promastigote forms of *L. amazonensis* and *L. chagasi*. It is important to detach that against the *ortho*-adduct 93c presented the minor IC_{50} values of 7.65 μM to *L. amazonensis* and 10.14 μM to *L. chagasi* (Table 7, entry 3).

In the same article,[51] quantum calculations, using the density functional theory (DFT) on B3LYP/6–311++G(d,p) as level of calculation, were performed and it was observed that the conformational minimum for the MBHA **70c** (Fig. 21) also shows the nitro group out of the plane of the aromatic ring (calculated dihedral angle = 23.98°), which may or affect the interaction with a possible active site into an enzyme or change the redox potential of this compound, as suggested in previous article.[47]

Is well known and already referenced in this review that bioreduction of nitro groups plays an important role on the activity of biologically active nitroaromatic compounds[52] and electrochemical methods are useful tools to simulate in vivo metabolic processes,[53–57] The electrochemical experiments with methyl 2-[*p*-nitrophenyl(hydroxy)methyl]acrylate (**14**) were performed by Goulard and Almeida's research group in 2007.[34] The primary reduction (E_{PC1}) behavior in aprotic medium was typical of nitroaromatics along with an additional wave related to the reduction of the acrylate function. These electrochemical results helped the understanding of the anticancer activity of **14**.

In 2012, Vasconcellos's research group described an electrochemical studies in aprotic media (DMF + TBAP 0.1 mol L^{-1}), using Cyclic Voltammetry (CV), Differential Pulse Voltammetry (DPV), and Square Wave Voltammetry (SWV) of twelve Morita–Baylis–Hillman adducts (MBHA) with significant leishmanicidal activity (Fig. 22).[58] In this article the optimized geometries were also obtained by conformational studies (Fig. 23) and the HOMO, LUMO, molecular hardness (N) and atomic charges (Q_N) values in nitrogen on nitro groups, were obtained (Table 8).

In this work, Vasconcellos's group has not found a clear relationship between LUMO energies itself and the reduction potentials (Table 8) of the nitro group attached to the aromatic ring of MBHA. However, according to Paula et al.,[59] when HOMO and LUMO values were used to calculate the molecular hardness, a more relevant parameter regarding to molecular reactivity could be obtained. These correlations could be verified on the isomeric MBHA (Table 8).[38,46,50] It is worth noting that there is a relationship between the values of Epc_1 with the calculated values of hardness to their isomeric compounds, and the corresponding IC_{50} values (Table 8). Note that in almost all cases, the *ortho*-NO_2 substituted

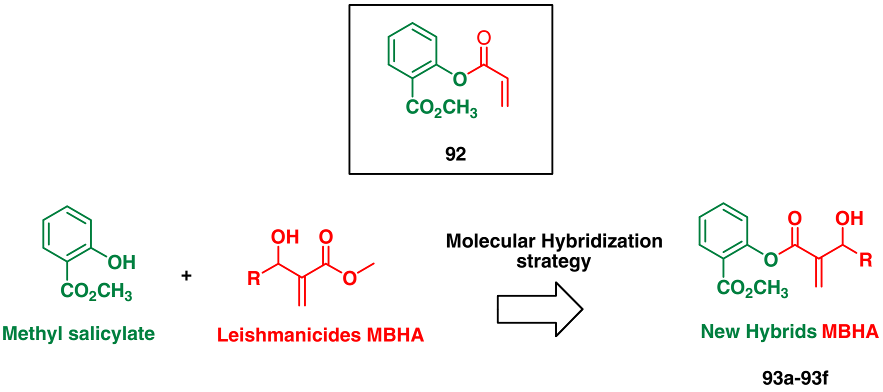
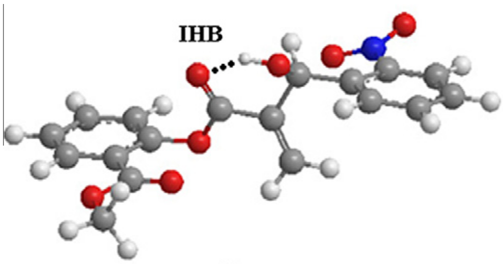


Figure 20. Molecular hybridization strategy on design of MBHA **93a–93f**.

Table 7
In vitro Leishmanicidal activity of MBHA **93a–93g**

Entry	MBHA	R	IC_{50} (μM) *L. amazonensis*	IC_{50} (μM) *L. chagasi*
1	**93a**	*p*-$(NO_2)C_6H_4$	11.34	57.34
2	**93b**	*m*-$(NO_2)C_6H_4$	22.86	40.64
3	**93c**	*o*-$(NO_2)C_6H_4$	7.65	10.14
4	**93d**	4-C_5H_4N	23.83	33.35
5	**93e**	3-C_5H_4N	31.15	38.69
6	**93f**	*p*-$(Br)C_6H_4$	22.00	43.03
7	**93g**	2-$C_{10}H_7$	9.00	41.38



93c

Figure 21. Conformational minimum of **93c** calculated from DFT theory on B3LYP/6–311++G(d,p).

MBH adducts are softer, present most positive atomic charge in nitrogen atom on the NO_2 group, and are the most leishmanicidal compounds. The results obtained in this article are a significant piece of knowledge in the search for comprehension of the possible mechanisms of action of these compounds. Against, in this work the α,β-unsaturated ester and nitrile moieties seem to be crucial in the mechanism of action of these compounds, especially in regards to biological nucleophilic targets of Leishmania, can be classified as pharmacophoric groups. The presence of a seven-membered ring intramolecular hydrogen bond (IHB) in the MBHA *ortho*-substituted seems to be also an important requirement for the remarkable bioactivities of these adducts in comparison to their respective isomers.

In another recent study reported the antimalarial activity of twenty-one MBHA derived the reaction between 2-chloroquinoline-3-carboxaldeídos and activated alkenes.[60] The quinolinecarboxaldehydes were prepared from anilides using a classical Vilsmeier–Haack reaction. All adducts were screened on antimalarial activity in vitro against *Plasmodium falciparum*. Most Significant adducts synthesized also exhibited antimalarial activity.[60]

4.3. Synthetics potentialities of the MBHA to the discovery of new 'one-pot' drugs

The synthesis of new congener series compounds having structures designed to act in a selected pathology is one of the most common strategies in medicinal chemistry. For this purpose, the possibility of obtaining shorter, cheaper and more efficient synthesis using ecofriendly synthetic protocols is widely obtained using the MBHA synthesis.

Recently, 20 MBHA (Fig. 24) were easily synthesized in moderated yields (50–70%) by Bhat and Singh[61] from different aromatic aldehydes and activated vinyl derivatives. These adducts, which are differently substituted 3-hydroxy-2-methylene-3-phenylpropionic acid derivatives, were screened for their antimicrobial activity in vitro by the serial dilution method. Many of these molecules displayed potent antibacterial and antifungal activities (Table 9).

This corroborates recent example of the great diversity of possibilities for molecular construction (almost infinite!) in one-steps procedures, which can be considered the *dream* of any industrial process. Then, we can note that the easily 'one-pot' synthesis from

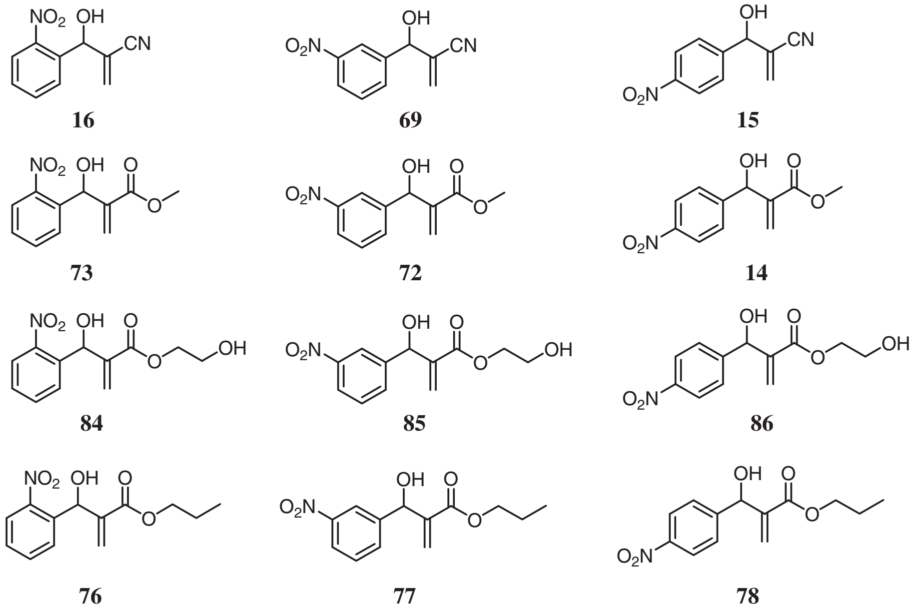
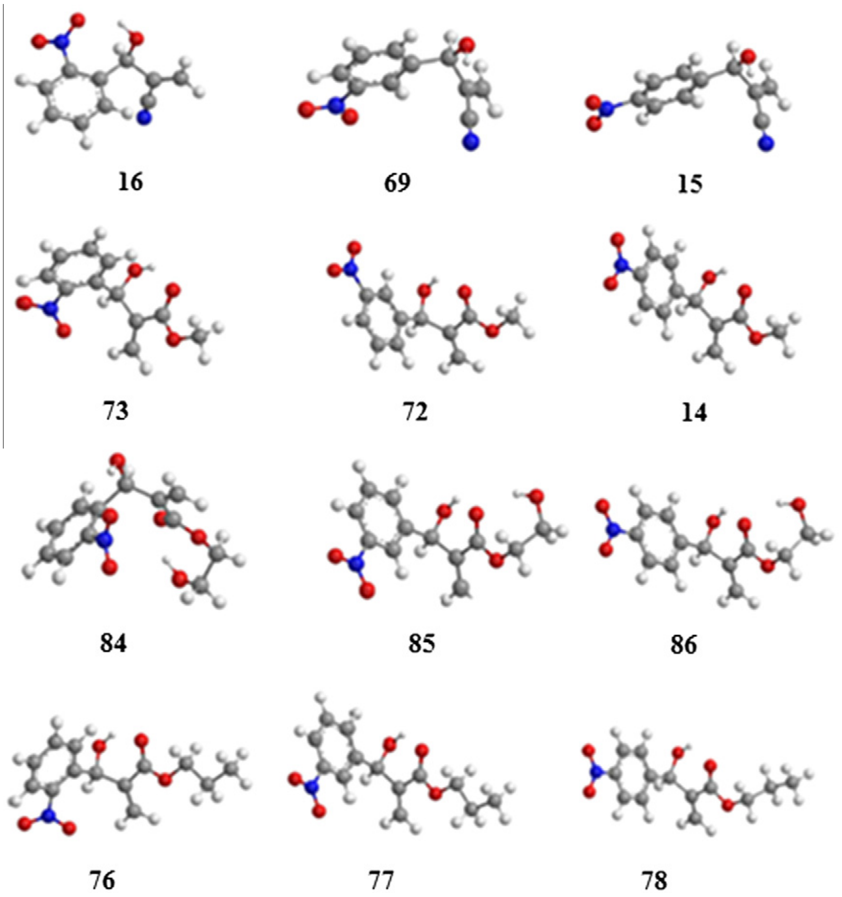


Figure 22. Twelve Morita–Baylis–Hillman adducts electrochemically studies.[58]



16 69 15

73 72 14

84 85 86

76 77 78

Figure 23. Conformational minima of 12 MBHA calculated from HF/6–31 +G(d)/PCM on DMF simulations.

Table 8
Correlation of calculated frontier orbitals, molecular hardness, charge of MBHA nitrogen atoms and IC_{50} on promastigotes of *L. amazonensis*[38,46,50]

MBHA	HOMO (eV)	LUMO (eV)	*N*[a]	[b]Q_N	Epc_1 (V)	IC_{50} (μM)[d]
16	−0.36546	+0.04060	−0.162430	+0.219	−0.944	62.00
69	−0.36309	+0.03556	−0.163765	+0.123	−1.028	238.27
15	−0.36622	+0.03495	−0.165635	+0.114	−1.029	128.27
73	−0.35704	+0.04747	−0.154785	+0.112	−1.061	50.08
72	−0.35713	+0.03776	−0.159685	+0.091	−1.062	451.58
14	−0.36295	+0.03774	−0.162605	+0.105	−1.084	196.16
84	−0.36218	+0.04327	−0.159455	+0.288	−1.014	20.52
85	−0.35741	+0.03703	−0.160190	+0.130	−1.077	64.57
86	−0.36322	+0.03754	−0.16284	+0.103	−1.056	53.03
76	−0.35681	+0.04742	−0.154695	+0.106[c]	−1.009	28.38
77	−0.35674	+0.03744	−0.159650	+0.124	−1.063	72.23
78	−0.36275	+0.03783	−0.162460	+0.104	−1.058	52.04

[a] N = molecular hardness.
[b] Q_N = Mulliken charges of nitrogen atoms of NO_2 groups.
[c] An exception.
[d] Promastigotes of *L. amazonensis*.[38,46]

low-cost starting materials along with potent antimicrobial activity of these molecules provide the lead for further improvement of activity and reflect the possibility of therapeutic use. In a particular way, the MBHA presenting *o*, *m* or *p*-nitro, *o*-chloro-, *p*-chloro, *p*-fluoro- and *o,p*-dichloro-substituents in the phenyl ring improved the potentiality as antibacterial and/or antifungal bioactivity.[61]

It is worth also highlighting two very recent articles based on this strategy.[62,9] Bases on the reported, there is an important relationship between the hydrophilicity/lipophilicity and the anti-parasitic activity of drugs, for example, that increasing the solubility in water or using cationic amphiphilic drugs (CADs) tends to increase anti-leishmaniasis and antimalarial activities[63,64]

In the first article,[62] Vasconcellos's group described the design and the microwave-promoted efficiently the synthesis of new monoacylglycerols (MAGs), the MBHA **106**–**111** (Fig. 25). Their strategy presented was based on the introduction of hydrophilic portion derived from the glycerol, as an important factor in water solubility increase of MBHA. All MAGs steps preparations were promoted by microwave irradiations, a very efficient and *green* methodology[65] used to obtain improvement in yields and rates of organic reactions and that has even more attracting the attention of industrial laboratories.

In the second article[9] it was reported by Vasconcellos's group the improved *green* one-pot synthesis to 24 anti-parasitic

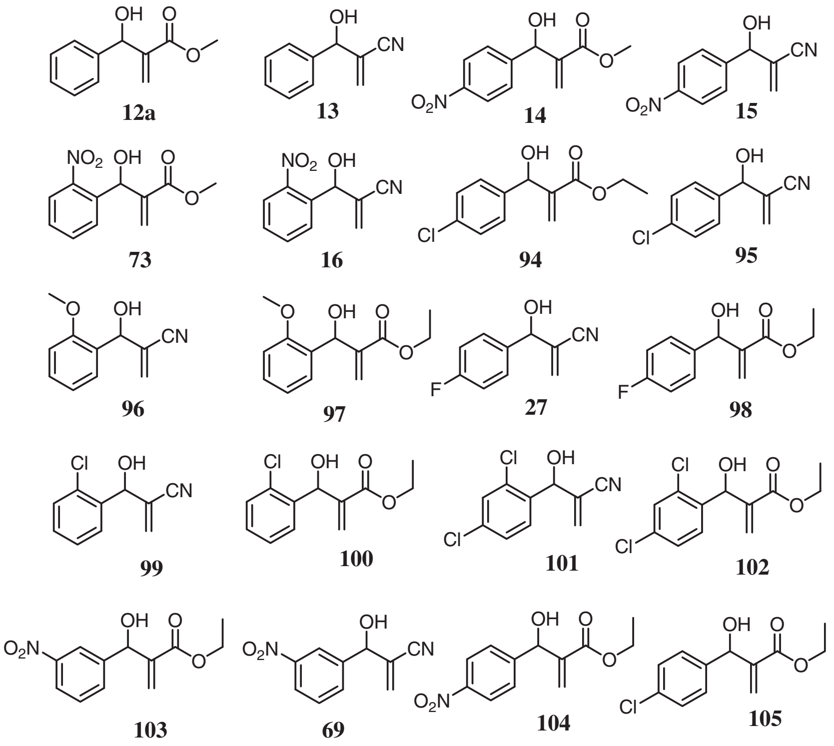


Figure 24. Twenty MBHA were synthesized and bio-evaluated by Bhat and Singh.[61]

Table 9
Minimum inhibitory concentration (MIC)[a] of MBHA studies by Bhat and Singh.[61]

MBHA	*Staphylococcus aureus*	*Corynebacterium diphtheriae*	*Klebsiella pneumoniae*	*Escherichia coli*	*Aspergillus niger*	*Candida albicans*
12a	–	25	30	22	–	–
13	20	20	21	19	–	–
14	16	14	18	17	–	13
15	15	15	20	17	12	12
73	16	14	18	17	11	12
16	15	15	20	17	11	13
94	18	16	18	15	11	12
95	16	19	18	16	12	13
96	–	–	25	24	12	–
97	–	–	22	21	–	12
27	18	18	20	17	11	13
98	20	19	18	16	14	15
99	18	18	18	16	14	13
100	18	18	18	16	14	13
101	16	15	15	18	13	11
102	18	17	18	20	11	15
103	16	14	18	16	13	14
69	16	14	18	17	14	10
104	18	18	17	18	12	11
105	18	18	16	20	13	12
Standard[b]	21	19	20	19	13	15

[a] $\mu g\ mL^{-1}$.

[b] Chloramphenicol and nystatin were used as references for antibacterial and antifungal tests, respectively.

Morita–Baylis–Hillman adducts (Fig. 26) using microwave irradiation at 80 °C or conventional protocol at 0 °C on free-solvent conditions. Most of these compounds were obtained in quantitative yields (100%) during 1.5–10 min of irradiation.

About the influence of the linked-groups on aromatic ring, it was observed that the diversity of substituent could lead to different effects in biological activity. In order to adducts containing the nitro group, we observed that these compounds are often more active, not only against parasitic diseases such as malaria, leishmaniasis and Chagas disease, as well as antimicrobial and antifungal. We can therefore conclude that the nitro group could be classified as a pharmacophore, whose mechanism of nitrocompounds are well known in the literature regarding these diseases.[52] As the difference of activity between regioisomers, the nitrocompounds have different reduction potentials, a fact which makes more active than the other (better ease of reduction to RNO_2-radical). Moreover, halogen groups connected on the aromatic ring leads to a change in the adducts lipophilicity (log*P*) and the

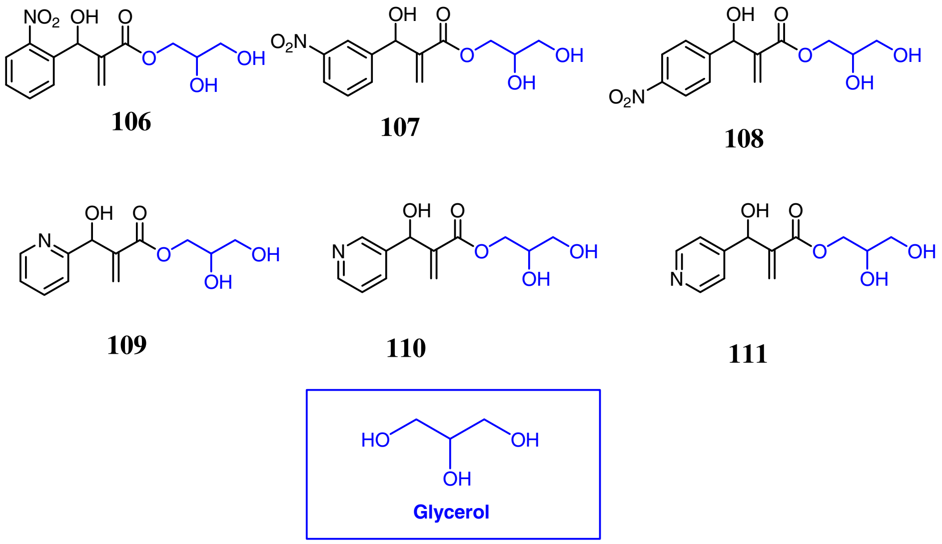


Figure 25. New monoacylglycerols (MAGs) as potential anti-parasitic compounds.

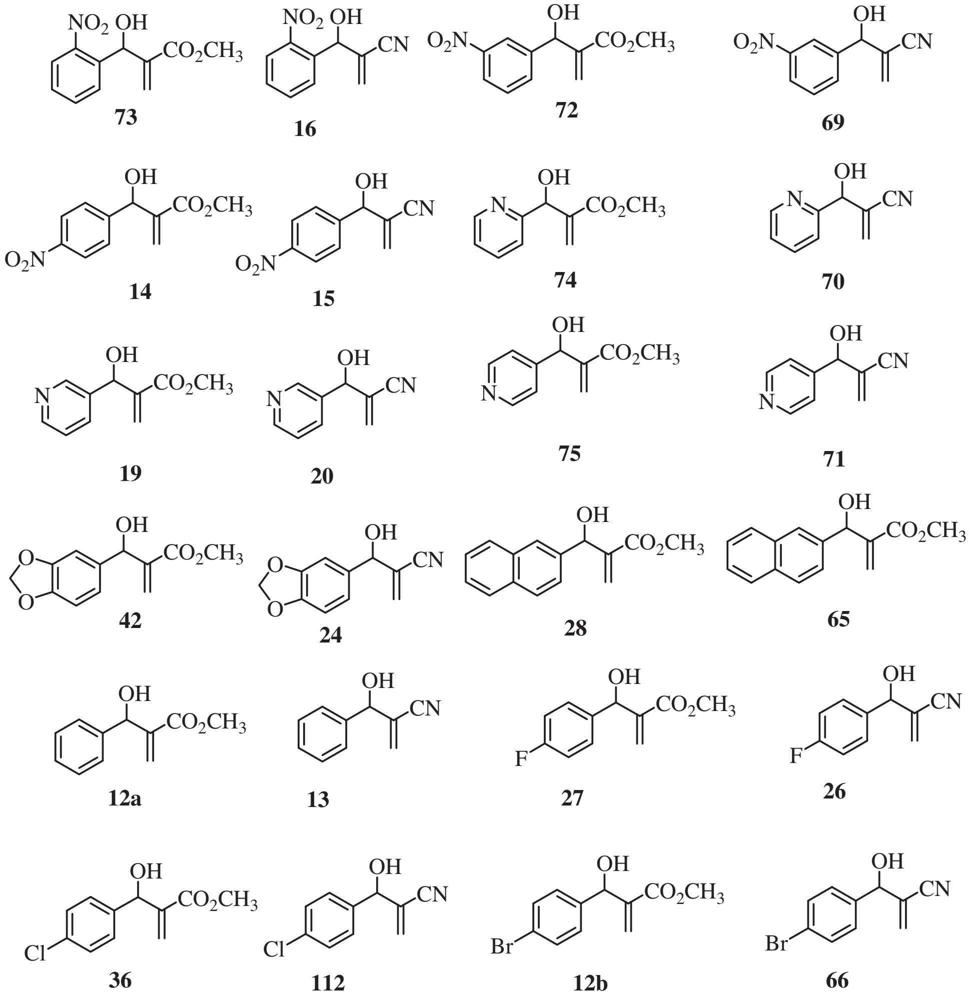


Figure 26. One-pot green synthesis to 24 anti-parasitic Morita–Baylis–Hillman adducts.

mechanism must be different from those suggested nitrocompounds. It is now a challenge to study the pharmacodynamics (PD) and pharmacokinetics (PK) for the various series of similar MBHA.

It is also very important to notice that Morita–Baylis–Hillman reaction generate chiral compounds. The bioevaluation of enantiomerically pure adducts it becomes necessary according to the Food and Drugs Administration (F.D.A.) requirements.[66,67] Some methods of solving kinetic and biotransformation enzymes are now being apply to MBHA is showing attractive ways to obtain enantiomerically pure bioactive MBHA.[68–70] Curiously, although some methods of asymmetric induction have been reported in recent years, such as the use of chiral, Michael acceptors chiral, asymmetric organocatalysts,[71] in the best of our knowledge no MBHA were bio-evaluated up to now in their enantiomerically pure forms. We believe this is a most persecuted target at the moment.

5. Conclusion

The simple MBHA have become an important class of bioactive compounds already presenting diversified biological activities as antimalarial, molluscicide, leishmanicidal, antichagasic, antitumoral, antifungal, antibacterial and herbicide. Recent applications of medicinal chemistry strategies in the design of new drug candidates for the MBHA are gaining space in literature. Now the preparation of MBHA can be performed in a single synthetic step, efficiently, with several challenges in these syntheses depending on the additives and reaction conditions, a fact that lead to the high chemoselectivity, in a short time of reactions and ecofriendly synthetic protocols. Strategies such as molecular hybridization, bioisosterism (classical and non-classical), and other strategies, that become to be more frequent in the search for new 'drug-adducts'.

Although investigations on possible biological mechanisms of action of these compounds are still in preluding stages, important structure–activity relationship analysis (SAR) and a preliminary 2D-QSAR study[72] have already been made and, of course, will certainly lead to a rational search for new bioactive MBHA.

Besides this, we believe that there is not single biological mechanism of action for all MBHA. Due to the versatility of MBHA structures, each congener series (e.g., the aryl-nitro compounds, pyridines, halo-aryl among others) should have different therapeutic targets (pharmacodynamics) as well as different metabolic routs (pharmacokinetics), which further extends the challenge of seeking more rationally increased selectivity index[50] of these compounds.

Finally, this easily form to design compounds specifically for a pathology make chemical synthesis of MBHA in a new and promising strategy to the discovery of new drugs.

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