



Iron(II) promoted direct synthesis of dibenzo[*b,e*]oxepin-11(6H)-one derivatives with biological activity. A short synthesis of doxepin



Jimena Scoccia^a, M. Julia Castro^{a,b}, M. Belén Faraoni^a, Cecilia Bouzat^b, Víctor S. Martín^c, Darío C. Gerbino^{a,*}

^a INQUISUR, Departamento de Química, Universidad Nacional del Sur (UNS)-CONICET, Avenida Alem 1253, 8000, Bahía Blanca, Argentina

^b INIBIBB, Departamento de Biología, Bioquímica y Farmacia, Universidad Nacional del Sur (UNS)-CONICET, Camino La Carrindanga km 7, 8000, Bahía Blanca, Argentina

^c IUBO, Departamento de Química Orgánica, Universidad de La Laguna, C/Astrofísico Francisco Sánchez 2, 38206, La Laguna, Tenerife, Spain

ARTICLE INFO

Article history:

Received 31 January 2017

Received in revised form

22 March 2017

Accepted 29 March 2017

Available online 31 March 2017

Keywords:

Synthetic methodology

Dibenzo[*b,e*]oxepin-11(6H)-ones

Intramolecular acylation

Doxepin

Anthelmintic activity

ABSTRACT

A novel and efficient synthesis of dibenzo[*b,e*]oxepin-11(6H)-ones by direct intramolecular *ortho*-acylation from readily available 2-(phenoxy)methylbenzoic acids was developed. The method takes advantage of a newly developed cooperative system consisting of sustainable FeCl₂ and Cl₂CHOCH₃ as the key components. This methodology is compatible with a wide variety of functional groups in good to excellent yields and high regioselectivity. The synthetic application of new protocol was extended to the synthesis of known tricyclic drug doxepin as well as a small library of oxepin based derivatives. For the first time, the obtained dibenzo[*b,e*]oxepinone derivatives were evaluated for their biological activities on the free-living nematode *Caenorhabditis elegans* as an effective and cost-efficient model system for anthelmintic discovery.

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

Helminthiasis, also known as worm infection, is a serious problem worldwide resulting in high human morbidity and enormous economic losses in livestock,¹ especially in tropical and subtropical countries. Anthelmintic drugs are used for the control of parasitic infections caused by helminths. With the increasing incidence of drug resistance and the high cost of existing pharmacological agents, the search for new antiparasitic drugs of synthetic origin is imperative.² *Caenorhabditis elegans* is a free-living nematode naturally found in soils of temperate climate, which has become a model organism for parasitic nematode research. It is also an excellent system for the screening of compounds with potential anthelmintic activity, because it is inexpensive, readily available, and easy to work.³ In addition, *C. elegans* has extensively used to investigate nematode behavior, locomotion, reproduction and death.⁴

Natural products play an important role in drug development, particularly in antineoplastic, antibiotics and antiparasitic drugs.⁵

Their structural diversity is a source of inspiration for drug discovery and the preparation of analogs as simplified, synthetically more accessible and stable models are broadly described in the literature.⁶ In this context, the tricyclic dibenzo[*b,e*]oxepin-11(6H)-one scaffold also known as “doxepinone”, emerges as an interesting synthetic target. In this respect, a large number of compounds having this privileged structure present relevant biological activities, such as antidepressant, anxiolytic, anticholinergic, antihistaminic,⁷ antipsychotic,⁸ analgesic, antipyretic, anti-inflammatory⁹ and antitumor drugs (Fig. 1).¹⁰ The dibenzo[*b,e*]oxepin-11(6H)-one motif containing natural products, such as chaetones **I** and **II**, showed remarkable cytotoxic and antimicrobial activities.¹¹ Interestingly, chaetone **II** also exhibited antitumor activity against gastric cancer cells BGC823.¹² Moreover, the metabolite pestalachloride **B** displayed significant antifungal activities against different plant pathogens.¹³ Dibenzo[*b,e*]oxepinones, isoxepac and skepinone-type of synthetic origin were identified as potential therapeutic agents for the treatment of inflammatory diseases, such as rheumatoid arthritis (RA), psoriasis, and Crohn's disease.¹⁴ In addition, these pharmacophores units are very important in medicinal chemistry due to their proved therapeutic properties.

The biological versatility exhibited by dibenzo[*b,e*]oxepinones

* Corresponding author. Tel./fax: +54 291 4595187.

E-mail address: dgerbino@uns.edu.ar (D.C. Gerbino).

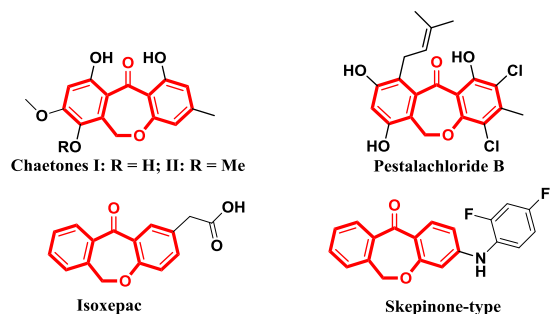


Fig. 1. Representative structures of dibenzo[*b,e*]oxepin-11(6H)-ones of biological interest.

and their congeners makes them very attractive targets for synthetic chemists.

Accordingly, the development of efficient methodologies for the construction of dibenzo[*b,e*]oxepin-11(6H)-one unit has represented a considerable synthetic challenge in the field of organic synthesis. Even though the synthesis of this framework represents a growing field due to the requirements of medicinal chemistry researches, a limited number of approaches for their synthesis has been developed to date.¹⁵ Among them, the two most common approaches for the synthesis of dibenzo[*b,e*]oxepinones are: (a) intramolecular C–O bond formation via Williamson ether synthesis¹⁶ and (b) cyclodehydration or intramolecular Friedel–Crafts acylation reaction of intermediates with a preformed aryl benzyl ether bond.¹⁷ However, they often suffer from a variety of disadvantages, such as poor yields, severe side reactions, high reaction temperature, prolonged reaction time, requirement of expensive reagents, low tolerance of functional groups^{15a,18} and poor regioselectivity. Similarly, another protocol under much milder reaction in the presence of trifluoroacetic anhydride has been developed.¹⁹ More recently, a new Parham cyclization methodology has been developed for the preparation of diaryl fused oxepinones. This strategy involves the generation of functionalized aryllithiums by bromine–lithium exchange, followed by intramolecular cyclization onto an electrophilic nitrile functional group.²⁰

Doxepin is a dibenzo[*b,e*]oxepine tricyclic with a tertiary amine chemical structure, which is marketed as a mixture of geometric isomers in a ratio of *Z:E* = 15:85. It acts by inhibiting the reuptake of serotonin and norepinephrine at chemical synapses. Its primary use is in the treatment of depression²¹ and it is also occasionally used in treating anxiety disorders and insomnia. As result of their therapeutic importance, doxepin and its congeners are interesting targets for chemical synthesis. Surprisingly, we found few precedents in the scientific literature of the total synthesis of this drug.²²

Herein, we describe the development of a novel and efficient synthetic strategy for the generation of a small library of dibenzo[*b,e*]oxepinones by direct intramolecular acylation of 2-(phenoxy-methyl)benzoic acids by using FeCl₂ and Cl₂CHOCH₃. To the best of our knowledge, this is the first report of the construction of seven membered oxygen heterocycles employing iron (II) and dichloromethyl methyl ether as cooperative system under mild and simple conditions. The interest and utility of our methodology was successfully applied as a key transformation in the synthesis of tricyclic drug doxepin.

Based on our experience in the biological evaluation of anti-parasitic agents²³ and for the purpose of expanding the spectrum of pharmacological action of dibenzo[*b,e*]oxepin-11(6H)-one scaffold, we decided to test all synthesized dibenzo[*b,e*]oxepinones derivatives for their anthelmintic activities using as the experimental model the nematode *C. elegans*.

2. Results and discussion

2.1. Chemistry

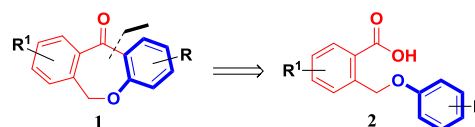
In recent studies, Kong-Wang and co-workers²⁴ established an interesting intramolecular acylation of benzyl esters by using the combined system of FeCl₃ with Cl₂CHOCH₃. This novel reactive system offered an efficient approach to the privileged structure xanthone,²⁵ which is structurally closely related to our target dibenzo[*b,e*]oxepin-11(6H)-one. However, this protocol is subjected to some limitations, such as non-availability of starting materials and low tolerance of electron-withdrawing functional groups. Inspired by this work, and in order to develop an operationally simple synthesis of the diaryl fused oxepin-11(6H)-one core, we decided to study the course of the direct intramolecular acylation of readily available 2-(phenoxy-methyl)benzoic acids by using different Lewis acids and dichloromethyl methyl ether (DCME). The strategic concept of our synthesis is summarized in Scheme 1.

The required starting materials for the synthesis of dibenzo[*b,e*]oxepinones type **1** can easily be obtained by treating substituted phthalide **I** with different sodium phenoxides derivatives **II** in DMF by modifications to known procedures (see ESI for experimental details).^{15a,f} An alternative synthetic route to access the substrates type **2** involves a Williamson synthesis between methyl 2-(bromomethyl)benzoate derivatives **III** and substituted phenols **II** followed by acid hydrolysis (Scheme 2).

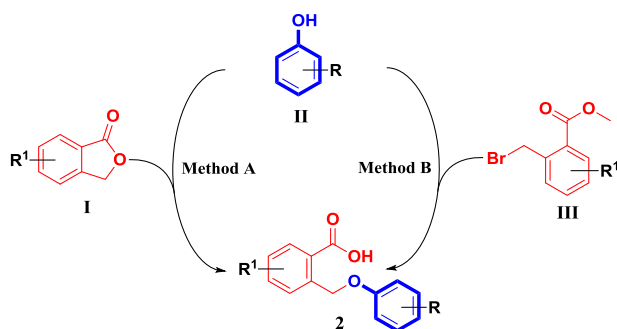
We started our study by choosing 2-((3-methoxyphenoxy)methyl)benzoic acid (**2c**) as model substrate to optimize the reaction conditions. These results are shown in Table 1.

Because of our active interest and experience in the area of green catalysis,^{25b} we first focused our research on the direct intramolecular acylation of **2c** in the presence of environmentally friendly FeCl₃ and DCME, following the protocol reported by Kong-Wang and co-workers.²⁴ It was observed that the reaction did not initiate at room temperature or even heating at reflux by using the cooperative system FeCl₃ with DCME in the presence of dichloromethane as solvent (Table 1, entries 1 and 2). On the other hand, FeBr₃ was also ineffective in attending this reaction under similar conditions (Table 1, entry 3). Unfortunately, increasing the loading of catalyst to 1 equivalent was ineffective for the present transformation, recovering the starting material **2c** (Table 1, entry 4). Moreover, when the amount of DCME was increased to 1.5 equivalents for 24 h, only the substrate **2c** was detected in the crude reaction (Table 1, entry 5). However, to our surprise the reaction was achieved in absence of FeCl₃ by using 1 equivalent of DCME albeit with a poor yield of only 20% (Table 1, entry 6). Further increasing the amount of DCME did not improve the yield of desired dibenzo[*b,e*]oxepin-11(6H)-one (Table 1, entry 7).

Based on the above studies, we decided carry out a systematic screening of the reaction conditions by treating the model substrate **2c** with various Lewis acid²⁶ in the presence of DCME in dichloromethane at room temperature (Table 1). As shown in the Table, we found that FeCl₂ and ZnCl₂ led to the best results (Table 1, entries 13 and 14) while other commercially available catalysts including SnCl₄, AlCl₃, CuCl₂, SnCl₂ and MgCl₂ showed less or no efficiency in terms of chemical yields (Table 1, entries 8–12). Taking into account

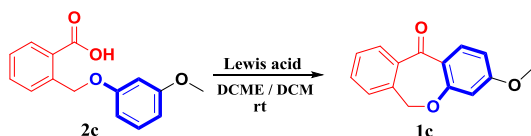


Scheme 1. Retrosynthetic analysis for dibenzo[*b,e*]oxepin-11(6H)-one framework.



Scheme 2. Preparation of 2-(phenoxymethyl)benzoic acids **2**. **Method A** (**2a–2h**): NaH (1.5 equiv), DMF, reflux, 24 h; then 1 N NaOH, 1 M HCl; **Method B** (**2i–2l**): K_3PO_4 (2 equiv), toluene, reflux, 5 h; then KOH, methanol, reflux.

Table 1
Optimization of the reaction conditions.^a



Entry	Lewis acid (equiv)	DCME (equiv)	Time (h) ^b	Yield (%) ^c
1	FeCl ₃ (0.6)	1.0	24	NR ^d
2	FeCl ₃ (0.6)	1.0	24 ^e	NR ^d
3	FeBr ₃ (0.6)	1.0	24	NR ^d
4	FeCl ₃ (1.0)	1.0	24	NR ^d
5	FeCl ₃ (0.6)	1.5	24	NR ^d
6	—	1.0	24	20
7	—	1.5	24	18
8	SnCl ₄ (0.6)	1.0	24	NR ^d
9	AlCl ₃ (0.6)	1.0	24	10
10	CuCl ₂ (0.6)	1.0	3	42
11	SnCl ₂ (0.6)	1.0	2	52
12	MgCl ₂ (0.6)	1.0	24	NR ^d
13	ZnCl ₂ (0.6)	1.0	2	80
14	FeCl₂ (0.6)	1.0	2	90
15	FeCl ₂ (0.6)	—	24	NR ^d
16	FeCl ₂ (0.6)	1.5	5	90
17	FeCl ₂ (0.6)	0.5	5	43
18	FeCl ₂ (0.4)	1.0	5	40
19	FeCl ₂ (0.8)	1.0	2	80
20	FeCl ₂ (0.6)	1.0	24 ^f	69
21	FeCl ₂ (0.6)	1.0	24 ^g	74

^a **Standard reactions conditions:** substrate **2c** (1 mmol), dichloromethyl methyl ether (DCME), in dichloromethane (0.1 M) at room temperature under argon.

^b Time reaction monitored by TLC and GC-MS.

^c Quantified by GC analysis using internal standard method.

^d NR: no reaction.

^e Reaction was conducted in DCM at reflux.

^f Reaction was carried out in toluene at room temperature.

^g Reaction was carried out in 1,2-dichloroethane (DCE) at room temperature.

the results summarized in Table 1, we choose the Lewis acid FeCl₂ for being the most efficient catalyst for the desired transformation. Control experiments were performed to prove the necessity of the coexistence of the catalyst FeCl₂ and the agent Cl₂CHOCH₃. The experimental results showed that the presence of DCME is crucial for the success of the reaction (entry 15). When the amount of DCME was decreased to 0.5 equivalent, a pronounced decrease was observed (i.e., 43%, Table 1, entry 17). Both the increase and the decrease of catalyst loading were not effective in improving yields of the desired transformation (Table 1, entries 18 and 19). Further increase of DCME from 1.0 to 1.5 equivalent did not improve the yield of **1c** (Table 1, entry 16). From the loading of iron (II) chloride,

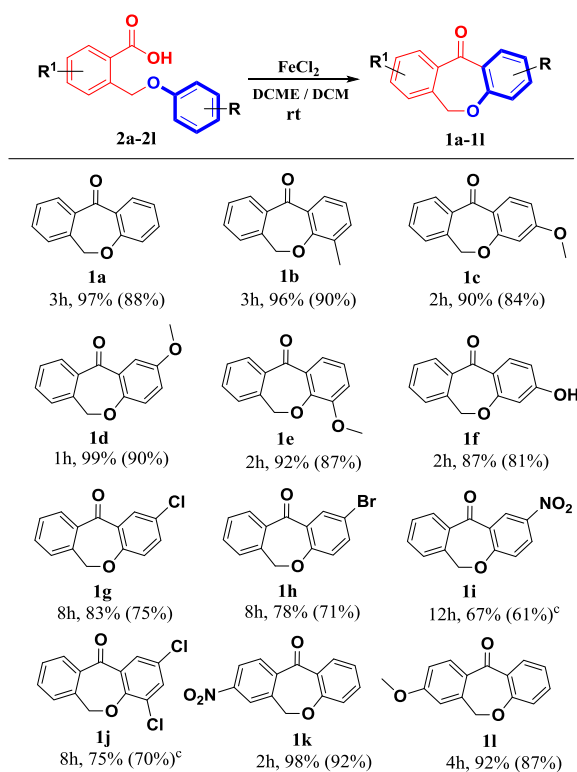
it could be shown that 0.6 equivalent of FeCl₂ was the optimal choice (Table 1, entry 14 regarding entries 18 and 19). On other hand, the screening of the reaction solvent demonstrated that dichloromethane (Table 1, entry 14) was superior in comparison to toluene and 1,2-dichloroethane (Table 1, entries 20 and 21). These combined studies demonstrated that 0.6 equivalent of environmentally friendly FeCl₂ by using 1.0 equivalent of DCME in the presence of dichloromethane at room temperature exhibited the highest efficiency for the direct intramolecular acylation from **2c**.

In order to extend the scope and the general efficiency of our methodology, we also applied this protocol to the synthesis of twelve functionalized dibenzo[*b,e*]oxepinones **1a–1l** under the optimized conditions (Table 2).

The results illustrated in Table 2 indicate that the present methodology is compatible with the presence of a wide variety of functional groups in the substrates **2**, including nitro, bromo, chlorine, alkoxy, alkyl, and a free phenolic hydroxyl group, affording a set of substituted dibenzo[*b,e*]oxepinones **1a–1l** in very good to excellent yields. Gratifyingly, treatment of compound **2k** bearing a strong electron-withdrawing group nitro led to **1k** in high yield. The acylation reaction of the starting materials with electron-donating substituents (**2b–2f**, and **2l**) proceeded under the optimized reaction conditions in very good yields (**1b–1f** and **1l**). It should be noted, that by using our protocol allowed the synthesis of tricyclic fused rings starting from 2-(phenoxymethyl)benzoic acids **2** bearing electron-withdrawing groups **1g–1k**, thus overcoming one of the limitations reported by other authors.^{15a,f} The oxepinone **1i** was formed very slowly in the presence of only FeCl₂ (0.6 equiv), but the reaction yield was improved to 61% by an increase in catalyst loading (1 equiv) in the presence of 1,2-dichloroethane at reflux. In this case, we think that the need to use 1 equivalent of Lewis acid could be related to that part of equivalent is preferably coordinated with the strong *meta*-director NO₂, leaving to the rest available to react with the corresponding substrate, thus generating carbocation, which promotes intramolecular acylation desired.²⁷ To our satisfaction, treatment of compound **2j** bearing two electron-withdrawing groups chlorine, afforded **1j** in good yield. The intramolecular acylation showed total *para* regioselectivity for the substrates containing a *meta*-substituent in the phenolic ring (**1c** and **1f**). The observed selectivity could be attributed in terms of a higher thermodynamic stability of the *para* regioisomer with respect to the *ortho* isomer. This reasoning would be in line with the fact that the acylation reaction could occur at the less sterically hindered *ortho*-C–H bond of the 2-(phenoxymethyl)benzoic acid derivatives used as precursors (**2c** and **2f**).

A comparison of our procedure with the typically employed strategies to perform this kind of *ortho*-acylation reaction revealed that the target dibenzo[*b,e*]oxepin-11(6H)-one is obtained in much more efficient in terms of yields when employing our simple and practical protocol (Table 3). In general, the existing methodologies employ drastic conditions such as phosphorus pentoxide-ethanol^{28a,9b} (Table 3, entry 1), polyphosphoric acid^{9b} (Table 3, entry 2), trifluoroacetic anhydride²⁹ with or without BF₃·Et₂O (Table 3, entry 4). However, our protocol substantially differs from these latter (Table 3, entry 5) in avoiding the use of large amounts of toxic acid chloride like thionyl chloride^{9b} (Table 3, entry 3), long reaction times, high temperatures and the generation of significant quantities of waste upon quenching of the reaction mixtures, that adversely impact their suitability for a potential scalability. In addition, our strategy uses simple precursors without need of previous activation. On the other hand, the present process allows a greater tolerance of functional groups in both rings of the starting material and greater operational simplicity than the methodologies reported to date.

Under these mild conditions, no acylation side-products were

Table 2Scope for the synthesis of functionalized dibenzo[*b,e*]oxepin-11(6H)ones.^a

^a **Reaction conditions:** substrate **2** (1 mmol), FeCl₂ (0.6 equiv), DCME (1 equiv), in dichloromethane (0.1 M) at room temperature under argon. Time reaction monitored by TLC and GC-MS. ^b Quantified by GC analysis using internal standard method. Isolated yield after purification (in parentheses). ^c Reaction was conducted in 1,2-dichloroethane (DCE) at reflux in the presence of FeCl₂ (1 equiv).

Table 3Comparison of the current methodology with some protocols previously reported for the synthesis of dibenzo[*b,e*]oxepin-11(6H)ones.

Entry	Reaction conditions	Time (h)	Yield (%) ^a	Ref
1	P ₂ O ₅ (exc.)/EtOH/sulfolane, reflux	5–12	20–64	28a
2	polyphosphoric acid (exc.), 100 °C	3–12	38–53	9b
3	SOCl ₂ (exc.)/DCE/AlCl ₃ (1 equiv), reflux	2–18	40–79	15a
4	Trifluoroacetic anhydride (2 equiv), DCM, reflux	4–10	41–86	29a
5	FeCl₂ (0.6 equiv)/DCME (1 equiv)/DCM, rt	1–12	61–92	Current work

^a Isolated yield after purification.

detected arising from cooperative system FeCl₂ and DCME, which is not typically employed in Friedel-Crafts acylations. The work-up and isolation of crude product consisted of operational simplicity by simple washing with water followed by extraction with DCM and subsequent treatment with aqueous saturated NaHCO₃, then the combined organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. Finally, the desired product was purified by column chromatography using silica gel 60 or recrystallized from ethanol. The structures of all dibenzo[*b,e*]oxepinones **1a–1l** were confirmed on the basis of their spectroscopic data, as provided in the Experimental section.

Having proved the efficiency and reliability of our methodology to access the dibenzo[*b,e*]oxepin-11(6H)-one framework, we sought to extend the present protocol to the synthesis of the known

drug doxepin.

The classic approach for the synthesis of doxepin uses the ethyl ester of 2-phenoxyethyl benzoic acid as starting material, which is easily synthesized by reacting ethyl 2-bromomethylbenzoate with phenol in the presence of a base.^{22d} The resulting ester is hydrolyzed into 2-phenoxyethylbenzoic acid, which is cyclized to dibenzo[*b,e*]oxepin-11(6H)-one (**1a**) by trifluoroacetic acid anhydride. Finally, the target molecule is obtained by reacting **1a** with 3-dimethylaminopropylmagnesium bromide and the subsequent dehydration of the resulting tertiary alcohol by hydrochloric acid. This strategy involved five steps of synthesis with an overall yield of 26%. A more recent stereoselective synthesis of doxepin was communicated by Luo et al.^{22f} Thus, the linear synthesis of doxepin required of six steps and proceeded with an overall yield of 7%

starting from 2-[(trimethylsilyl)ethynyl]benzyl bromide.

Simplified retrosynthetic analysis of doxepin **3** is summarized in Scheme 3. As a key consideration, we proceed to assemble the dibenzo[*b,e*]oxepin-11(6H)-one (**1a**) scaffold through a direct intramolecular acylation from 2-(phenoxymethyl)benzoic (**2a**) acid mediated by eco-friendly FeCl₂ and DCME.

The target 3-(dibenzo[*b,e*]oxepin-11(6H)-ylidene)-*N,N*-dimethyl propan-1-amine (**3**) was synthesized in three stages. In the first stage, the 2-(phenoxymethyl) benzoic acid (**2a**) was easily prepared by treating the commercial available isobenzofuran-1(3H)-one (**I**) with sodium phenoxide, which was obtained by reacting phenol (**II**) with NaH in the presence of DMF at reflux. The carboxylic acid **2a** was precipitated using a mineral acid solution. The key intermediate **1a** was cyclized by intramolecular acylation from **2a** by using FeCl₂ and dichloromethyl methyl ether (DCME) as cooperative system in the presence of dichloromethane at room temperature. Finally, the target molecule **3** was synthesized by reacting **1a** with 3-dimethylaminopropylmagnesium chloride and the subsequent dehydration of the resulting tertiary alcohol by hydrochloric acid at reflux in good yield (Scheme 4).

The proportion between (*E*) and (*Z*)-isomers in the crude product was 4 to 1. The structure elucidation of **3** was proved by its GC-MS, ¹H, and ¹³C NMR spectra analysis.

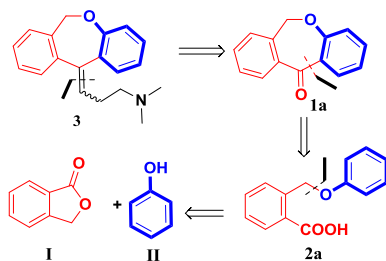
It should be noted that the (*E*)-isomer was easily separated by crystallization as maleate salt after treatment of **3** with an equivalent amount of maleic acid in dry ethanol.

This synthesis of **3** involves only three steps and proceeds with an overall yield of 44% starting from commercially available phthalide **I**, thus overcoming the best chemical yields reported by other authors^{22e,f} until now. Notably, most intermediates are crystalline solids and only one of the three steps required chromatographic purification. Thus, the synthesis of **3** could be performed on a multigram scale enabling us to also investigate some aspects of the reactivity.

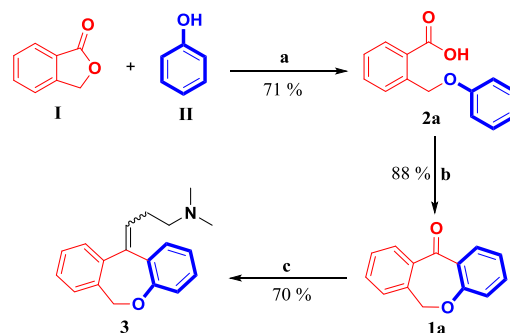
2.2. Anthelmintic activity

In a recent study, doxepin structurally related to our target dibenzo[*b,e*]oxepin-11(6H)-one, have been shown to have anthelmintic activity against the intestinal helminth *Ancylostoma ceylanicum* third-stage larvae (L3).³⁰ In this context, and considering the experience of our group in biological assays associated with this type of activity, added to the fact that there are no contributions in the scientific literature on such biological action, we sought to determine if our synthesized tricyclic scaffolds act as antiparasitic drugs. To this end, we used *C. elegans* as a model of helminthic parasites and measured their rapid effects on *C. elegans* mobility by the thrashing assay method.

The thrashing rate of wild-type worms in M9 buffer (plus 1% DMSO) was 204 ± 9.3/min. After a 10-min incubation period with compounds **1a–1l** and doxepin **3** (1 mM), a slight albeit statistically significant reduction in the thrashing rate was observed (Fig. 2).



Scheme 3. Retrosynthetic analysis to access the doxepin **3**.



Scheme 4. Total synthesis of doxepin **3**. Conditions: a) NaH (1.5 equiv), DMF, reflux, 24 h; then conc. HCl; b) FeCl₂ (0.6 equiv), DCME (1 equiv), DCM (0.1 M), rt, 3 h; c) 3-(*N,N*-dimethylamino) propylmagnesium chloride, toluene, 65 °C, 2 h; then conc. HCl, 1 h, reflux.

For these compounds, the thrashing rates varied between 60 and 84% with respect to the control condition. Interestingly, compound **1a** produced a much more significant effect on worm mobility, leading to a reduction of 80% of the thrashes/min at 1 mM after a 10-min exposure (Fig. 2).

When analyzed at a range of concentrations (30 μM–1.5 mM), compound **1a** produced a concentration-dependent decrease of the thrashing rate, with an IC₅₀ value of 389 ± 50 μM (Fig. 3).

Increasing the incubation period to 20 min in the presence of 1 mM compound **1a** produced complete paralysis of worms. Thrashing assays are useful to demonstrate short-term and rapid effects of compounds on the high-frequency *C. elegans* locomotion. In these assays, common anthelmintic drugs, such as levamisole, morantel and pyrantel (1 mM), have been shown to affect significantly the thrashing rates after 5–10 min in M9 solution, leading to a 90% reduction and producing paralysis of the majority of animals.³¹ Thus, we showed that dibenzo[*b,e*]oxepin-11(6H)-one **1a** produces similar effects to those mediated by widely-used anthelmintic drugs.

Previous reports showed that doxepin **3** produced 60% death of *A. ceylanicum*. However, in this work death was evaluated after 72 h exposure to the drug and, therefore, only long-term effects were considered.³⁰ In contrast, our assays evaluate short-term effects since worms are exposed to the drugs for only 10 min. Under these conditions, doxepin **3** produced a very slight anthelmintic effect on *C. elegans*. A short-term effect as the one observed for compound **1a**

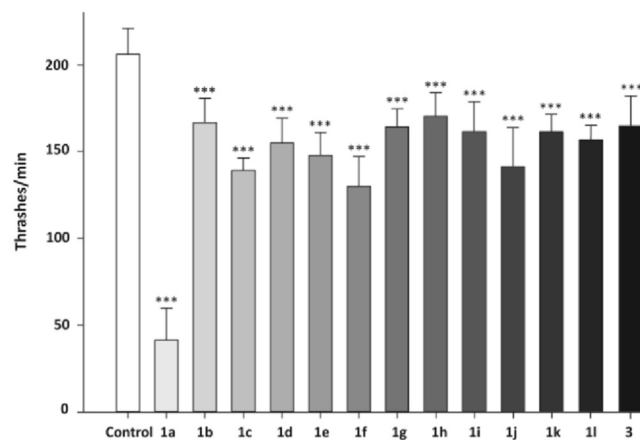


Fig. 2. Thrashing rates after 10 min incubation in M9 solution in the absence (control) or presence of a given compound (1 mM). Assays were performed on three separate days for each drug. Twenty animals were tested in each assay. ***P < 0.001.

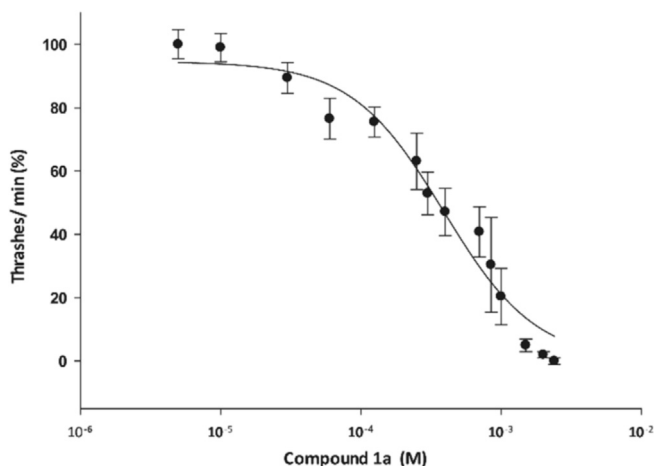


Fig. 3. Dose-response curve for dibenzo[b,e]oxepin-11(6H)-one **1a**. Thashing rates were plotted as a percentage of the control condition in the absence of the drug. Values are mean percentages \pm SD derived from three trials performed on separate days. All experiments were performed at 20–22 °C.

might be mediated by ion channels, such as ligand-gated ion channels, which are involved in neuromuscular function and worm locomotion. Typical anthelmintics, such as pyrantel, morantel, and levamisole, act by this mechanism.²¹ In general terms, it was observed that the introduction of functionality to the tricyclic ring system **1a** was detrimental to biological activity. Interestingly, a marked decrease in activity was observed for doxepin **3**, suggesting that the carbonyl group was important for the activity. Thus, the pharmacophore appeared to be the scaffold **1a**, which may be considered as a candidate anthelmintic drug. Although levamisole and pyrantel are effective antiparasitic drugs, the increment of drug resistance of nematodes to these anthelmintic drugs as well as to the limited number of available drugs has become a global concern for veterinary and human health. Indeed, the combination of drugs is emerging as a strategy tending to fight against the increase in anthelmintic resistance. Thus, the identification of novel drugs and pharmacological targets is urgently required, which enhances the importance of the anthelmintic action of compound **1a** here reported. Thus, future work will focus on the identification of the pharmacological target by which compound **1a** exerts its antiparasitic activity. Once this target is known, derivatization of the active compound to increase its potency and efficacy will be rationally planned.

3. Conclusions

In the current research, we have developed a new and complementary methodology for the simple construction of dibenzo[b,e]oxepin-11(6H)-ones from readily available 2-(phenoxyethyl) benzoic acids by using FeCl_2 and $\text{Cl}_2\text{CHOCH}_3$ as an efficient cooperative system. Unlike other existing standard Friedel-Crafts approaches, our strategy showed an excellent tolerance to diverse substituent groups makes the reaction a fairly general synthesis protocol to diaryl fused oxepin-11(6H)-ones. Due to the modularity, operational simplicity, and reliability it is likely that the method will find future exploitation in the synthesis of compound libraries, and therefore have an impact on to the field of medicinal chemistry. We are currently working on the design of some specific experiments aimed at shed light on the exact reaction mechanism. To probe the general application of our protocol, we elaborated a short and scalable synthesis of tricyclic drug doxepin **3** from commercial available phthalide. The scalability of the process, the simple

reaction conditions, and the low cost of the starting materials, make this new total synthesis transferable to the pharmaceutical industry. The synthetic accessibility and significant antiparasitic activity exhibited by dibenzo[b,e]oxepin-11(6H)-one **1a** might be a promising lead in the search for novel anthelmintic drugs. It is noteworthy that this is the first report of anthelmintic activity of this class of oxygenated tricyclic compounds using the free-living nematode *Caenorhabditis elegans* as an experimental model system. Future studies may be directed to identify its mechanism of action and drug target.

4. Experimental section

4.1. General

All operations were performed under an argon atmosphere using standard Schlenk techniques. Solvents were dried and distilled in accordance with standard procedure.³² Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light and/or using 5% phosphomolybdic acid in ethanol. All ^1H and ^{13}C NMR spectra were recorded at room temp. in CDCl_3 , $\text{DMSO}-d_6$ or $\text{Acetone}-d_6$ on a Bruker Avance ARX-300 spectrophotometer. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) using the residual solvent resonance (CDCl_3 : 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR; $\text{DMSO}-d_6$: 2.50 ppm for ^1H NMR and 39.50 ppm for ^{13}C NMR; $\text{Acetone}-d_6$: 2.09 ppm for ^1H NMR, 30.60 and 205.87 ppm for ^{13}C NMR). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; brs = broad signal). IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer in the ATR mode at room temp. Melting points were determined using a Büchi 510 apparatus and are not corrected. Mass spectra (EI) were obtained at 70 eV on an Agilent CG-78903 instrument equipped with a MS-5977 A MSD selective mass detector. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a GC Shimadzu (GC-14B) with a flame ionization detector equipped with a HP-5MS column (30 m \times 0.25 mm \times 0.25 μm) using nitrogen as carrier gas. High resolution mass spectra were recorded on Thermo Fisher LTQ Orbitrap XL, (for EI) and a Finnigan MAT 95 (for ESI). Flash column chromatography was performed using Macherey Nagel MN Kieselgel 60M (0.040–0.063 mm/230–240 mesh ASTM). All starting materials were of the best available grade (Aldrich, Merck, Acros or TCI) and were used without further purification. (CAUTION) Dichloromethyl methyl ether is a corrosive and acute toxic reagent.

4.2. General procedure for synthesis of 2-(phenoxyethyl) benzoic acids (**2a-2l**)

4.2.1. Method A (**2a-2h**)

Substituted phenol (16 mmol) was added to a stirred suspension of sodium hydride (24 mmol) in anhydrous DMF (20 mL). Upon cessation of dihydrogen evolution, phthalide (15 mmol), dissolved in the minimum amount of benzene (CAUTION) and the mixture heated under reflux for 24 h. The cooled solution was poured into ice water (50 mL) and acidified with conc. HCl. The formed precipitate was filtered, washed with water and subsequently dissolved in dichloromethane (50 mL). The organic layer was washed successively with 20% aq. Na_2CO_3 (3 \times 20 mL) and water (3 \times 20 mL), and dried over Na_2SO_4 . The solvent was distilled off to give a solid. The crude product was used in the next step without further purification.

4.2.1.1. 2-(phenoxyethyl)benzoic acid (2a**)**^{15a}. Isolated yield: 65% (white solid, 550 mg, 2.41 mmol); mp 112–114 °C; ^1H NMR (CDCl_3 ,

300 MHz) δ 5.53 (s, 2H), 6.95–7.03 (m, 3H), 7.26–7.34 (m, 2H), 7.40–7.45 (m, 1H), 7.63 (dt, J = 7.6, 1.3 Hz, 1H), 7.81–7.84 (m, 1H), 8.18 (dd, J = 7.9, 1.2 Hz, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 68.2, 115.1, 121.2, 126.4, 127.4, 127.5, 129.7, 131.9, 133.8, 140.9, 158.8, 172.2; IR (KBr) ν [cm^{-1}] = 3440, 3051, 2897, 1685, 1594, 1243. HRMS (EI) m/z = 228.0786 calcd for $\text{C}_{14}\text{H}_{12}\text{O}_3$, found 228.0781.

4.2.1.2. 2-((*o*-tolylloxy)methyl)benzoic acid (2b)³³. Isolated yield: 58% (white solid, 910 mg, 3.75 mmol); mp 137–139 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 2.40 (s, 3H), 5.57 (s, 2H), 6.88–6.93 (m, 2H), 7.15–7.21 (m, 2H), 7.44 (t, J = 7.4 Hz, 1H), 7.66 (t, J = 7.4 Hz, 1H), 7.90 (d, J = 7.7 Hz, 1H), 8.21 (d, J = 7.7 Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 16.6, 68.1, 111.7, 120.8, 126.4, 127.0, 127.1, 127.2, 127.3, 130.9, 131.8, 133.8, 141.3, 156.8, 172.7. IR (KBr) ν [cm^{-1}] = 3438, 3058, 2898, 1696, 1595, 1240. HRMS (EI) m/z = 242.0943 calcd for $\text{C}_{15}\text{H}_{14}\text{O}_3$, found 242.0948.

4.2.1.3. 2-((3-methoxyphenoxy)methyl)benzoic acid (2c). Isolated yield: 43% (light brown solid, 1.67 g, 6.47 mmol); mp 105–107 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 3.71 (s, 3H), 5.47 (s, 2H), 6.44–6.54 (m, 3H), 7.09–7.18 (m, 3H), 7.34 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 55.4, 68.3, 101.7, 106.7, 107.3, 126.5, 127.4, 127.5, 130.1, 131.9, 133.8, 140.8, 160.0, 161.0, 172.6. IR (KBr) ν [cm^{-1}] = 3441, 3055, 2901, 1691, 1594, 1234. HRMS (EI) m/z = 258.0892 calcd for $\text{C}_{15}\text{H}_{14}\text{O}_4$, found 258.0896.

4.2.1.4. 2-((4-methoxyphenoxy)methyl)benzoic acid (2d)³⁴. Isolated yield: 60% (white solid, 486 mg, 1.88 mmol); mp 163–165 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 3.72 (s, 3H), 5.46 (s, 2H), 6.85–6.88 (m, 2H), 6.93–6.96 (m, 2H), 7.42–7.47 (m, 1H), 7.62 (dt, J = 7.5, 1.4 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 8.07 (dd, J = 7.8, 1.4 Hz, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 55.9, 69.4, 115.5, 116.6, 128.2, 128.4, 129.3, 131.8, 133.3, 141.0, 153.9, 155.1, 168.4. IR (KBr) ν [cm^{-1}] = 3431, 3050, 2899, 1693, 1598, 1231. HRMS (EI) m/z = 258.0892 calcd for $\text{C}_{15}\text{H}_{14}\text{O}_4$, found 258.0897.

4.2.1.5. 2-((2-methoxyphenoxy)methyl)benzoic acid (2e). Isolated yield: 54% (light brown solid, 1.20 g, 4.70 mmol); mp 123–125 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 3.08 (s, 3H), 5.65 (s, 2H), 6.89–6.95 (m, 4H), 7.38–7.43 (m, 1H), 7.59–7.64 (m, 1H), 7.86 (d, J = 7.9 Hz, 1H), 8.16–8.19 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 55.1, 69.3, 112.0, 114.1, 121.0, 121.6, 126.3, 127.3, 127.4, 131.8, 133.9, 141.0, 148.2, 149.7, 172.6. IR (KBr) ν [cm^{-1}] = 3440, 3052, 2901, 1692, 1595, 1230. HRMS (EI) m/z = 258.0892 calcd for $\text{C}_{15}\text{H}_{14}\text{O}_4$, found 258.0896.

4.2.1.6. 2-((3-hydroxyphenoxy)methyl)benzoic acid (2f)³⁵. Isolated yield: 53% (light brown solid, 34 mg, 1.39 mmol); mp 113–115 °C; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 5.34 (s, 2H), 6.43–6.34 (m, 3H), 7.05–7.10 (m, 1H), 7.42 (dt, J = 7.5, 2.0 Hz, 1H), 7.62–7.57 (m, 2H), 7.89–7.91 (m, 1H), 7.2 (brs, 1H), 12.9 (brs, 1H); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ 62.2, 102.2, 108.1, 110.1, 126.3, 127.3, 130.5, 131.0, 131.8, 139.9, 157.1, 160.3, 172.7. IR (KBr) ν [cm^{-1}] = 3441, 3055, 2900, 1695, 1598, 1235, 1230. HRMS (EI) m/z = 244.0736 calcd for $\text{C}_{14}\text{H}_{12}\text{O}_4$, found 244.0740.

4.2.1.7. 2-((4-chlorophenoxy)methyl)benzoic acid (2g)^{15a}. Isolated yield: 54% (light brown solid, 86 mg, 3.29 mmol); mp 160–162 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 5.44 (s, 2H), 6.85 (dt, J = 9.0, 3.4 Hz, 2H), 7.17 (dt, J = 9.0, 3.4 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 7.52–7.57 (m, 1H), 7.69 (d, J = 7.9 Hz, 1H), 8.08–8.11 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 68.6, 116.4, 126.1, 126.6, 127.5, 127.7, 129.5, 131.9, 133.8, 140.3, 157.4, 172.0. IR (KBr) ν [cm^{-1}] = 3439, 3050, 2901, 1694, 1599, 1234. HRMS (EI) m/z = 262.0397 calcd for

$\text{C}_{14}\text{H}_{11}\text{ClO}_3$, found 262.0401.

4.2.1.8. 2-((4-bromophenoxy)methyl)benzoic acid (2h). Isolated yield: 65% (white solid, 504 mg, 1.65 mmol); mp 171–173 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 5.52 (s, 2H), 6.95–7.01 (m, 2H), 7.43–7.49 (m, 3H), 7.62 (dt, J = 7.6, 1.4 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 8.08 (dd, J = 7.7, 1.0 Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 69.1, 113.4, 120.1, 128.4, 128.5, 131.9, 132.2, 133.4, 140.1, 159.1, 168.3. IR (KBr) ν [cm^{-1}] = 3439, 3050, 2901, 1694, 1599, 1234. HRMS (EI) m/z = 305.9892 calcd for $\text{C}_{14}\text{H}_{11}\text{BrO}_3$, found 305.9896.

4.2.2. Method B (2i–l)

To a solution of 6.0 g (0.04 mol) of methyl 2-methylbenzoate derivatives in 38 mL of chloroform, 7.5 g (0.042 mol) of *N*-bromosuccinimide and 0.078 g of benzoyl peroxide were added and carefully warmed up to 65 °C until reaction started. Then the mixture was refluxed for 5 h. After cooling down to room temperature, the deposit of succinimide was filtered. The solvent was removed under reduced pressure and the crude product was used in the next step without further purification. To a solution of functionalized methyl 2-(bromomethyl)benzoate (6.55 mmol), substituted phenol (8.5 mmol), K_3PO_4 (16.4 mmol) and toluene 20 mL were added to Schlenk under argon. The resulting solution was stirred to 110 °C for 5 h. The progress of the reaction was monitored by TLC. The mixture was extracted with EtOAc, washed with water, brine and the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was used in the next step without further purification. To the solution of the ester (0.015 mol) in MeOH (73 mL), was added 13 mL aqueous KOH (20%) and refluxed at 80 °C for 5 h. MeOH was removed and the aqueous phase was washed with DCM. After acidifying with HCl (10%) the deposit was collected and washed with water.

4.2.2.1. 2-((4-nitrophenoxy)methyl)benzoic acid (2i). Isolated yield: 40% (white solid, 543 mg, 1.99 mmol); mp 143–145 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 5.69 (s, 2H), 7.21–7.24 (m, 2H), 7.48–7.53 (m, 1H), 7.62–7.68 (m, 1H), 7.74 (d, J = 7.8 Hz, 1H), 8.10–8.12 (m, 1H), 8.23–8.26 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 69.7, 116.1, 126.7, 128.8, 128.9, 129.6, 132.0, 133.5, 139.1, 142.6, 164.9, 168.3. IR (KBr) ν [cm^{-1}] = 3240, 2830, 1695, 1598, 1270. HRMS (EI) m/z = 273.0637 calcd for $\text{C}_{14}\text{H}_{11}\text{NO}_5$, found 273.0641.

4.2.2.2. 2-((2,4-dichlorophenoxy)methyl)benzoic acid (2j). Isolated yield: 96% (white solid, 455 mg, 1.50 mmol); mp 241–243 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 5.59 (s, 2H), 6.92–6.95 (m, 1H), 7.19 (dd, J = 8.7, 2.5 Hz, 1H), 7.40–7.48 (m, 2H), 7.68 (dt, J = 7.6, 1.3 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 8.19 (dd, J = 7.8, 1.2 Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 69.3, 114.7, 124.0, 126.1, 126.2, 127.3, 127.7, 127.8, 130.2, 132.0, 134.1, 139.9, 153.1, 172.2. IR (KBr) ν [cm^{-1}] = 3270, 2828, 1699, 1262. HRMS (EI) m/z = 296.0007 calcd for $\text{C}_{14}\text{H}_{10}\text{Cl}_2\text{O}_3$, found 296.0011.

4.2.2.3. 4-Nitro-2-(phenoxymethyl)benzoic acid (2k)^{15f}. Isolated yield: 68% (white solid, 464 mg, 1.70 mmol); mp 179–180 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 5.19 (s, 2H), 6.91–7.12 (m, 1H), 7.28–7.33 (m, 2H), 7.34–7.68 (m, 2H), 8.30 (dd, J = 7.5 Hz, 1H), 8.45 (dd, 1H), 8.23–8.26 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 67.4, 114.9, 121.5, 121.9, 125.1, 129.4, 129.5, 130.3, 135.6, 144.9, 149.3, 169.8. IR (KBr) ν [cm^{-1}] = 3340, 2880, 1691, 1600, 1524, 1495, 1270. HRMS (EI) m/z = 273.0637 calcd for $\text{C}_{14}\text{H}_{11}\text{NO}_5$, found 273.0642.

4.2.2.4. 4-Methoxy-2-(phenoxymethyl)benzoic acid (2l)^{15c}. Isolated yield: 88% (white solid, 454 mg, 1.76 mmol); mp 160–162 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 3.73 (s, 3H), 5.42 (s, 2H),

6.87–6.95 (m, 1H), 6.97–7.10 (m, 1H), 7.11–7.18 (m, 2H), 7.24 (dd, 1H), 7.26–7.34 (m, 2H), 7.95 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 55.3, 67.4, 111.5, 112.8, 114.4, 114.9, 121.5, 129.4, 131.1, 137.6, 149.3, 159.9, 168.8. IR (KBr) ν [cm^{-1}] = 3435, 3039, 2905, 1696, 1599, 1241. HRMS (EI) m/z = 258.0892 calcd for $\text{C}_{15}\text{H}_{14}\text{O}_4$, found 258.0896.

4.3. General procedure for synthesis of dibenzo[b,e]oxepin-11(6H)-ones (**1a–1l**)

Functionalized 2-(phenoxyethyl)benzoic acid (1.0 mmol), FeCl_2 (0.6 equiv), dichloromethyl methyl ether (1.0 equiv) (CAUTION), and CH_2Cl_2 (10 mL) were added to a Schlenk tube under argon. The resulting solution was stirred at room temperature until the completion of the reaction. The progress of the reaction was monitored by TLC and GC-MS. The reaction was quenched by addition of water. The mixture was extracted with CH_2Cl_2 , washed with aqueous saturated NaHCO_3 and then the combined organic layers were dried over anhydrous Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using silica gel 60 or recrystallized in ethanol.

4.3.1. Dibenzo[b,e]oxepin-11(6H)-one (**1a**)^{15a}

Isolated yield: 88% (white solid, 120 mg, 0.58 mmol, eluent: hexane/EtOAc 90:10); mp 65–67 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 5.19 (s, 2H), 7.04–7.15 (m, 2H), 7.35–7.38 (m, 1H), 7.44–7.58 (m, 3H), 7.90 (dd, $J = 7.6$, 1.3 Hz, 1H), 8.25 (dd, $J = 8.0$, 1.9 Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 73.7, 120.8, 122.2, 125.5, 127.9, 129.3, 129.6, 132.1, 132.8, 135.4, 135.7, 140.7, 161.4, 191.2. MS m/z : 210 (100), 181 (80), 152 (29), 89 (15), 76 (15), 63 (12). IR (KBr) ν [cm^{-1}] = 2921, 2870, 1653, 1456. HRMS (EI) m/z = 210.0681 calcd for $\text{C}_{14}\text{H}_{10}\text{O}_2$, found 210.0685.

4.3.2. 4-methyldibenzo[b,e]oxepin-11(6H)-one (**1b**)³⁶

Isolated yield: 90% (white solid, 170 mg, 0.75 mmol, eluent: hexane/EtOAc 90:10); mp 68–70 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 2.28 (s, 3H), 5.23 (s, 2H), 7.01 (t, $J = 7.7$ Hz, 1H), 7.35–7.39 (m, 2H), 7.43–7.49 (m, 1H), 7.55 (dt, $J = 7.5$, 1.2 Hz, 1H), 7.89 (dd, $J = 7.5$, 0.8 Hz, 1H), 8.10 (dd, $J = 8.3$, 1.4 Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 16.8, 73.6, 121.6, 125.5, 127.6, 129.3, 129.4, 129.5, 130.0, 132.7, 135.9, 136.4, 140.7, 159.7, 191.6. MS m/z : 224 (100), 209 (25), 195 (36), 181 (34), 165 (19), 152 (20), 115 (6), 89 (19). IR (KBr) ν [cm^{-1}] = 3068, 2945, 2856, 1654, 1471, 808, 751. HRMS (EI) m/z = 224.0837 calcd for $\text{C}_{15}\text{H}_{12}\text{O}_2$, found 224.0832.

4.3.3. 3-methoxydibenzo[b,e]oxepin-11(6H)-one (**1c**)^{15c}

Isolated yield: 84% (light brown solid, 160 mg, 0.65 mmol, eluent: hexane/EtOAc 90:10); mp 135–137 °C; ^1H NMR (Acetone- d_6 , 300 MHz) δ 3.86 (s, 3H), 5.25 (s, 2H), 6.54 (d, $J = 2.5$ Hz, 1H), 6.74 (dd, $J = 9.1$, 2.5 Hz, 1H), 7.34 (s, 1H), 7.47–7.52 (m, 1H), 7.57–7.63 (m, 1H), 7.84–7.87 (m, 1H), 8.15 (d, $J = 9.1$ Hz, 1H); ^{13}C NMR (Acetone- d_6 , 75 MHz) δ 56.7, 74.8, 104.6, 111.7, 129.5, 129.3, 130.4, 130.5, 133.8, 134.8, 137.4, 141.9, 164.7, 166.9, 189.6. MS m/z : 240 (100), 211 (22), 197 (30), 168 (10), 141 (12), 115 (11), 89 (11). IR (KBr) ν [cm^{-1}] = 3065, 2953, 1723, 1490, 853. HRMS (EI) m/z = 240.0786 calcd for $\text{C}_{15}\text{H}_{12}\text{O}_3$, found 240.0781.

4.3.4. 2-methoxydibenzo[b,e]oxepin-11(6H)-one (**1d**)³⁷

Isolated yield: 90% (white solid, 80 mg, 0.35 mmol); mp 96–98 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 3.85 (s, 3H), 5.15 (s, 2H), 6.97–7.00 (m, 1H), 7.07–7.11 (m, 1H), 7.34–7.36 (m, 1H), 7.44–7.58 (m, 2H), 7.69–7.70 (m, 1H), 7.93 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 55.9, 74.1, 112.5, 122.1, 124.4, 125.6, 127.8, 129.2, 129.9, 132.9, 136.2, 140.0, 154.6, 156.1, 190.6. MS m/z : 240 (100), 225 (38),

211 (18), 197 (20), 169 (11), 141 (22), 115 (28), 89 (13). IR (KBr) ν [cm^{-1}] = 3072, 2962, 2921, 1720, 1486, 829, 796. HRMS (EI) m/z = 240.0786 calcd for $\text{C}_{15}\text{H}_{12}\text{O}_3$, found 240.0782.

4.3.5. 4-methoxydibenzo[b,e]oxepin-11(6H)-one (**1e**)³⁸

Isolated yield: 87% (light brown solid, 40 mg, 0.17 mmol); mp 70–72 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 3.83 (s, 3H), 5.23 (s, 2H), 6.98–7.02 (m, 2H), 7.29–7.31 (m, 1H), 7.39 (dt, $J = 7.6$, 1.2 Hz, 1H), 7.48 (dt, $J = 7.5$, 1.3 Hz, 1H), 7.74 (dd, $J = 7.2$, 2.7 Hz, 1H), 7.79 (dd, $J = 7.5$, 1.3 Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 56.5, 74.2, 116.2, 121.5, 123.0, 126.3, 127.9, 129.3, 129.4, 132.8, 135.3, 140.8, 150.7, 151.6, 191.5. MS m/z : 240 (100), 225 (11), 211 (26), 197 (27), 181 (22), 169 (15), 152 (16), 141 (20), 115 (28), 89 (18), 63 (11). IR (KBr) ν [cm^{-1}] = 3070, 2960, 2918, 1711, 1476, 829, 794. HRMS (EI) m/z = 240.0786 calcd for $\text{C}_{15}\text{H}_{12}\text{O}_3$, found 240.0780.

4.3.6. 3-hydroxydibenzo[b,e]oxepin-11(6H)-one (**1f**)

Isolated yield: 81% (brown solid, 110 mg, 0.50 mmol); mp 138–140 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 5.30 (s, 2H), 6.81–6.87 (m, 1H), 7.03–7.06 (m, 1H), 7.16 (d, $J = 6.5$ Hz, 1H), 7.38 (d, $J = 6.3$ Hz, 1H), 7.50–7.58 (m, 2H), 7.75 (d, $J = 7.8$ Hz, 1H), 7.94 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 74.8, 119.9, 122.6, 122.7, 128.0, 129.7, 130.0, 133.0, 134.2, 135.1, 140.5, 147.2, 148.4, 190.6. MS m/z : 226 (100), 197 (43), 181 (17), 164 (14), 152 (15), 141 (21), 115 (17), 89 (15). IR (KBr) ν [cm^{-1}] = 3432, 2966, 2922, 1650, 1270, 1106, 1023, 804. HRMS (EI) m/z = 226.0630 calcd for $\text{C}_{14}\text{H}_{10}\text{O}_3$, found 226.0635.

4.3.7. 2-chlorodibenzo[b,e]oxepin-11(6H)-one (**1g**)²⁰

Isolated yield: 75% (white solid, 140 mg, 0.57 mmol); mp 117–119 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 5.18 (s, 2H), 7.01 (d, $J = 8.8$ Hz, 1H), 7.35–7.43 (m, 2H), 7.48 (dt, $J = 7.6$, 1.1 Hz, 1H), 7.58 (dt, $J = 7.6$, 1.2 Hz, 1H), 7.89 (dd, $J = 7.6$, 1.0 Hz, 1H), 8.20 (d, $J = 2.7$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 73.9, 122.5, 126.4, 127.7, 128.0, 129.6, 129.8, 131.2, 133.2, 135.2, 135.5, 140.0, 159.9, 189.8. MS m/z : 246 (33), 244 (100), 217 (12), 215 (34), 209 (36), 181 (37), 152 (48), 89 (21), 76 (18), 63 (21). IR (KBr) ν [cm^{-1}] = 3071, 2956, 2923, 1646, 1470, 837, 825. HRMS (EI) m/z = 244.0291 calcd for $\text{C}_{14}\text{H}_9\text{ClO}_2$, found 244.0295.

4.3.8. 2-bromodibenzo[b,e]oxepin-11(6H)-one (**1h**)³⁹

Isolated yield: 71% (white solid, 130 mg, 0.46 mmol); mp 122–124 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 5.18 (s, 2H), 6.95 (d, $J = 8.7$ Hz, 1H), 7.37 (d, $J = 7.2$ Hz, 1H), 7.46–7.60 (m, 3H), 7.89 (d, $J = 7.5$ Hz, 1H), 8.35 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 73.9, 114.9, 122.9, 126.8, 128.1, 129.6, 129.8, 133.2, 134.3, 135.4, 138.0, 140.1, 160.4, 189.8. MS m/z : 290 (96), 288 (100), 261 (20), 259 (21), 209 (39), 181 (41), 152 (66), 89 (32), 76 (26), 63 (31). IR (KBr) ν [cm^{-1}] = 3074, 2958, 2930, 1646, 1470, 837, 760. HRMS (EI) m/z = 287.9786 calcd for $\text{C}_{14}\text{H}_9\text{BrO}_2$, found 287.9790.

4.3.9. 2-nitrodibenzo[b,e]oxepin-11(6H)-one (**1i**)

Isolated yield: 61% (light brown solid, 150 mg, 0.61 mmol, eluent: hexane/EtOAc 90:10); mp 151–153 °C. ^1H NMR (CDCl_3 , 300 MHz) δ 4.11 (s, 2H), 7.31–7.42 (m, 3H), 7.54 (dt, $J = 7.6$, 1.3 Hz, 1H), 7.90 (dd, $J = 7.6$, 0.9 Hz, 1H), 8.11–8.15 (m, 1H), 8.2 (d, $J = 2.6$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 77.4, 122.0, 124.0, 124.2, 127.5, 128.3, 133.2, 134.0, 134.3, 141.1, 145.2, 155.4, 164.3, 207.1. IR (KBr) ν [cm^{-1}] = 3052, 2957, 2929, 1654, 1590, 1260, 800. HRMS (ESI) m/z = 278.0430 calcd for $\text{C}_{14}\text{H}_9\text{NNaO}_4$ [$\text{M}+\text{Na}$] $^+$, found: 278.0426.

4.3.10. 2,4-dichlorodibenzo[b,e]oxepin-11(6H)-one (**1j**)

Isolated yield: 70% (white solid, 190 mg, 0.70 mmol, eluent: hexane/EtOAc 90:10); mp 138–140 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 5.30 (s, 2H), 7.41 (d, $J = 7.2$ Hz, 1H), 7.50 (dt, $J = 7.5$, 0.8 Hz, 1H), 7.58–7.63 (m, 2H), 7.87–7.90 (m, 1H), 8.13 (d, $J = 2.7$ Hz, 1H); ^{13}C

NMR (CDCl₃, 75 MHz) δ 72.6, 124.8, 125.4, 125.5, 126.3, 127.9, 128.0, 128.3, 131.6, 133.2, 133.3, 137.8, 153.8, 187.2; MS m/z : 282 (9), 280 (65), 278 (100), 251 (19), 249 (29), 245 (18), 243 (51), 217 (11), 215 (32), 186 (13), 152 (38), 89 (23), 63 (12). IR (KBr) ν [cm⁻¹] = 3068, 2955, 2926, 1652, 1467, 823, 813. HRMS (EI) m/z = 277.9901 calcd for C₁₄H₈Cl₂O₂, found 277.9905.

4.3.11. 8-nitrodibenzo[b,e]oxepin-11(6H)-one (**1k**)^{15f}

Isolated yield: 92% (light solid, 230 mg, 0.92 mmol, eluent: hexane/EtOAc 90:10); mp 179–181 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 5.45 (s, 2H), 7.12–7.21 (m, 2H), 7.61 (t, *J* = 7.6, 1.3 Hz, 1H), 7.95–8.01 (m, 2H), 8.52 (d, *J* = 2.6 Hz, 1H), 8.55 (s, 1H); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 70.6, 115.1, 123.1, 123.4, 125.1, 127.4, 129.3, 130.6, 133.2, 140.0, 140.8, 147.2, 157.1, 199.7. IR (KBr) ν [cm⁻¹] = 3050, 2956, 2927, 1653, 1591, 1260, 799. HRMS (ESI) m/z = 278.0430 calcd for C₁₄H₉NNaO₄ [M+Na]⁺, found: 278.0427.

4.3.12. 8-methoxydibenzo[b,e]oxepin-11(6H)-one (**1l**)^{15c}

Isolated yield: 87% (light solid, 210 mg, 0.87 mmol, eluent: hexane/EtOAc 90:10); mp 130–132 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.89 (s, 3H), 5.28 (s, 2H), 7.08 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.10–7.16 (m, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.58 (brs t, *J* = 7.6 Hz, 1H), 7.89 (t, *J* = 8.7 Hz, 1H), 8.20 (dd, *J* = 8.1, 1.3 Hz, 1H); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 55.6, 73.2, 113.1, 114.5, 120.6, 122.2, 125.5, 131.5, 131.8, 132.1, 135.2, 138.8, 160.7, 163.0, 187.7. MS m/z : 240 (100), 211 (20), 197 (27), 168 (12), 141 (11), 115 (10), 89 (12). IR (KBr) ν [cm⁻¹] = 3055, 2953, 2925, 1715, 1495, 851. HRMS (EI) m/z = 240.0786 calcd for C₁₅H₁₂O₃, found 240.0782.

4.4. Synthesis of 3-(dibenzo[b,e]oxepin-11(6H)-ylidene)-*N,N*-dimethylpropan-1-amine (**3**)

3-(*N,N*-dimethylamino)propylmagnesium chloride was prepared from magnesium turnings (0.04 mol) activated with iodine at 75 °C for 1 h. THF (1 mL), toluene (4 mL) and some drops of methyl iodide was added at 65 °C and stirred for 30 min 3-chloro-*N,N*-dimethylpropylamine (0.03 mol) in toluene (15 mL) was added slowly. After 30 min **1a** (0.02 mol) in 10 mL toluene was added. The reaction mixture was stirred vigorously at 65 °C for 2 h. Then, concentrated hydrochloric acid (20 mL) was added slowly (30 min) at 65 °C and the reaction mixture was stirred for 1 h. The organic phase was separated and the aqueous phase extracted with diethyl ether (200 mL). The aqueous phase was made alkaline with aqueous ammonia and extracted with diethyl ether. The organic phase was dried over anhydrous Na₂SO₄, filtered and the diethyl ether was removed under reduced pressure to give 190 mg (0.7 mmol, 70%) of **3** as a colourless oil. The ¹H NMR spectrum of the reaction crude product showed it to consist of a mixture the expected geometric *E*- (80%) and *Z*- (20%) isomers in different proportions. The majority (*E*)-diastereoisomer was easily separated by crystallisation of the corresponding maleate.^{22e} ¹H NMR (CDCl₃, 300 MHz) δ 2.60–2.74 (m, 4H), 2.70 (s, 6H), 4.80 (brs, 1H), 5.50 (brs, 1H),⁴⁰ 5.91 (t, *J* = 7.0 Hz, 1H), 6.75–7.40 (m, 8H); ¹³C NMR (CDCl₃, 75 MHz) δ 24.9, 42.4, 60.2, 73.7, 119.2, 121.2, 127.5, 127.9, 128.2, 128.3, 128.5, 128.8, 129.4, 130.3, 134.4, 141.1, 141.3, 155.2. MS m/z : 279 (40), 219 (22), 282 (25), 189 (30), 178 (40), 165 (45), 115 (25), 59 (50), 58 (100). IR (KBr) ν [cm⁻¹] = 3050, 3025, 1698, 1582, 1483, 1431. HRMS (EI) m/z = 279.1623 calcd for C₁₉H₂₁NO, found 279.1628.

4.5. Anthelmintic assays using *C. elegans*

The *C. elegans* wild-type (Bristol variety) strain was obtained from the *Caenorhabditis* Genetic Center, which is funded by the NIH National Center for Research Resources (NCRR). Nematodes were

raised at 21 °C under standard laboratory conditions on agar plates cultured with *Escherichia coli* (OP50).²³ Thrashing assays were used to measure worm motility essentially as described before.⁴¹ Worms were synchronously grown to early adult stage. Individual young adult *C. elegans* were placed in 100 μ L of M9 buffer (3 g/L KH₂PO₄, 6 g/L Na₂HPO₄, 5 g/L NaCl, 0.25 g/L MgSO₄·7H₂O) in the absence or presence of the compound under study (1 mM/DMSO 1%) in a 96-well microlitre plate. After 10 min, the number of thrashes were counted for 30 s. A single thrash was defined as a complete change in the direction of bending at the mid body. The experiments were repeated 3 times for each condition (20 worms tested each time). All assays were blind and carried out at 20–22 °C. Data are shown as mean \pm S.D. Statistical comparisons were done using the oneway ANOVA with Bonferroni's multiple comparison posttest. Thrashing rates lower than those of control worms with *p* < 0.05 were considered significant. The half-inhibition concentration, IC₅₀, was obtained from the curve resulting from the percentage of thrashes/min in the presence of compound **1a** respect to the buffer condition.

Acknowledgments

This work was generously supported by the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) and Universidad Nacional del Sur (UNS) from Argentina to DCG and CB, and a Grand Challenges Explorations Grant from Bill and Melinda Gates Foundation to CB (OPP1098404). CB and DCG are research members of CONICET. MBF is research member of CIC. JS and MJC thank the CONICET for a postdoctoral fellowship.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.tet.2017.03.085>.

References

- Waller PJ. *Int J Parasitol.* 1999;29:155–164.
- Mehlhorn H, Al-Quraishy S, Al-Rasheid KA, Jatzlau A, Abdel-Ghaffar F. *Parasitol Res.* 2011;108:1041–1046.
- Simpkin KG, Coles GCC. *J Chem Technol Biotechnol.* 1981;31:66–69.
- Thompson DP, Klein RD, Geary TG. *Parasitology.* 1996;113:S217–S238.
- Newman DJ, Cragg GM. *J Nat Prod.* 2012;75:311–335.
- (a) Molinski TF, Dalisay DS, Lievens SL, Saludes JP. *Nat Rev Drug Discov.* 2009;8:69–85; (b) Njardarson JT, Gaul C, Shan D, Huang XY, Danishefsky SD. *J Am Chem Soc.* 2004;126:1038–1040.
- (a) Bloom B. M., Tretter J. R. Belg. Patent 641 498, 1964. (b) Stach K, Bickelkaupt F. *Mon Chem.* 1962;93:896–904.
- Stach K. U.S. Patent 3 438 981, 1969.
- (a) Ueno K., Kubo S., Yoshioka T., Tagawa H., Shimada S., Kojima H., Tsukada H., Tsubolawa M. Jap. Patent 800 0377, 1980. (b) Ueno K, Kubo S, Tagawa H, et al. *J Med Chem.* 1976;19:941–946.
- King A. C., Chapel Hill, N. C. U.S. Patent 300 282, 1994.
- Shen K-Z, Gao S, Gao YX, et al. *Planta Med.* 2012;78:1837–1843.
- Junzhi Q, Xiaoxia L, Jiao F, et al. *Chem Abstr.* 2013;158:532348.
- Li E, Jiang L, Guo L, Zhang H, Che Y. *Bioorg Med Chem.* 2008;16:7894–7899.
- (a) Feldmann MB, Fionula M, Maini RN. *Annu Rev Immunol.* 1996;14:397–440; (b) Baur B, Storch K, Martz KE, et al. *J Med Chem.* 2013;56:8561–8578.
- (a) Sadek B, Limban C, Stecoza CE, Elz S. *Sci Pharm.* 2011;79:749–761; (b) Rudolf W, Baumeister U, Florea S, Nicolae A, Maior O. *Monatsh Chem.* 1999;130:1475–1480; (c) Andrews B, Bullock K, Condon S, et al. *Synth Commun.* 2009;39:2664–2673; (d) Richey RN, Yu H. *Org Process Res Dev.* 2009;13:315–320; (e) Kluge AF, Caroon JM, Unger SH, Ryley JF. *J Med Chem.* 1978;21:529–536; (f) Laufer SA, Ahrens GM, Karcher SC, Hering JS, Niess R. *J Med Chem.* 2006;49:7912–7915.
- (a) Zimmermann K, Waldmeier PC, Tatton WG. *Pure Appl Chem.* 1999;71:2039–2046; (b) For review, see: Olivera R, SanMartin R, Churrua F, Domínguez E. *Org Prep Proced Int.* 2004;36:297–330 (and references cited therein); (c) Hoyer H, Vogel M. *Monatsh Chem.* 1962;93:766–774.

17. (a) Harris TW, Smith HE, Mobley PL. *J Med Chem.* 1982;25:855–858;
(b) Nagai Y, Irie A. *J Med Chem.* 1982;25:1065–1070;
(c) Ong HH, Proffitt JA, Anderson VB, et al. *J Med Chem.* 1980;23:494–501;
(d) Manske RHF, Ledingham AE. *J Am Chem Soc.* 1950;72:4797–4799.
18. (a) Lednicher D. *Strategies for Organic Drug Synthesis and Design.* New York: Wiley Interscience; 1998:379–400;
(b) Li S, Chen H, Chen L, et al. *ARKIVOC.* 2008;2:172–182.
19. Kathryn R, Holger, U.S. Patent 042818, 2009.
20. Farrokh J, Campos C, Hunt DA. *Tetrahedron Lett.* 2015;56:5245–5247.
21. (a) Pinder RM, Brogden RN, Speight TM, Avery GS. *Drugs.* 1977;13:161–218;
(b) Midha KK, Hubbard JW, Mckay G, et al. *Eur J Clin Pharmacol.* 1992;42:539–544;
(c) Constantine JW, Scriabine A, Smith SG, McShane WK, Booher KDJ. *New Drugs.* 1964;38:249–257;
(d) Fulton-Kehoe D, Rossing DMA, Rutter C, Mandelson MT, Weiss NS. *Br J Cancer.* 2006;94:1071–1078 (and papers cited therein).
22. (a) Bloom B. M., Tretter J. R. U.S. Patent 420 851, 1969.(b) Schaumann W., Stach K. Ger. Patent 1 232 161, 1961. (c) Stach K, Bickelhaupt F. *Monatsh, Chem.* 1962;93:896, 895;
(d) Bickelhaupt F, Stach K, Thiel M. *Monatsh, Chem.* 1964;95:485–494;
(e) Jalander L, Oksanen L, Ahtinen J. *Synth Commun.* 1989;19:3349–3352;
(f) Xue C, Kung SH, Wu JZ, Luo FT. *Tetrahedron.* 2008;64:248–254.
23. (a) Rayes D, Flamini M, Hernando G, Bouzat C. *Mol Pharmacol.* 2007;71:1407–1415;
(b) Hernando G, Berge I, Rayes D, Bouzat C. *Mol Pharmacol.* 2012;82:550–560.
24. Jiang N, Li SY, Xie SS, et al. *RSC Adv.* 2014;4:63632–63641.
25. (a) Pinto MMM, Sousa ME, Nascimento MS. *Curr Med Chem.* 2005;12:2517–2538;
(b) Menéndez C, Nador F, Radivoy G, Gerbino DC. *Org Lett.* 2014;16:2846–2849.
26. Verbanac D, Jain SC, Jain N, et al. *Bioorg Med Chem.* 2012;20:3180–3185.
27. Shen Y, Liu H, Chen Y. *J Org Chem.* 1990;55:3961–3962.
28. (a) Aultz DE, Helsley GC, Hoffman D, McFadden AR, Lassman HB, Wilker JC. *J Med Chem.* 1977;20:66–70;
(b) Ueno K, Kubo S, Tagawa H, et al. *J Med Chem.* 1976;19:941–946.
29. (a) Hamer RRL, Tegeler JT, Kurtz ES, et al. *J Med Chem.* 1996;39:246–252;
(b) Kumazawa T, Ohshima E, Harakawa H, et al. *Chem Phar Bull.* 1991;39:2729–2733.
30. Keiser J, Panic G, Adelfio R, Cowan N, Vargas M, Scandale I. *Parasites Vectors.* 2016;9(376):1–10.
31. Sleight JN. *Biosci Horizons.* 2010;3:29–39.
32. Perrin DD, Amarego WLF. *Purification of Laboratory Chemicals.* Oxford: Pergamon; 1988.
33. Naveena CS, Poojary B, Arulmoli T, Manjunatha K, Prabhu A, Kumari NS. *Med Chem Res.* 2013;22:1925–1937.
34. Müller J, Limban C, Stadelmann B, et al. *Parasitol Int.* 2009;58:128–135.
35. Fiedler W., Neises B., Hachtel J. U.S. Patent 7 238 835, 2007.
36. Takizawa I, Morita O., Oiji Y., Hashimoto T. U.S. Patent 396 550, 1983.
37. Kurokawa M, Sato F, Masuda Y, et al. *Chem Pharm Bull.* 1991;39:2564–2573.
38. Guta R, Limban C, Missir AV, Caproiu MT, Nuta DCD. *Rev Chim Buchar.* 2011;62:606–609.
39. Siddegowda MS, Yathirajan HS, Ramakrishna RA. *Tetrahedron Lett.* 2012;53:5219–5222.
40. (a) Casarotto MG, Craik DJ. *J Pharm Sci.* 2001;90:713–721;
(b) Casarotto MG, Craik DJ, Munro SL. *Magn Reson Chem.* 1990;28:533–540;
(c) Wyatt DK, Roscher NM, Grady LT. *Appl Spectrosc.* 1986;40:538–542.
41. Jones AK, Rayes D, Al-Diwani A, et al. *J Biol Chem.* 2011;286:2550–2558.