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A novel and easy two-step, microwave-assisted method for the synthesis of halophenyl pyrrolo[2,3-*b*]quinoxalines via their pyrrolo precursors. Evaluation of their bioactivity

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ABSTRACT

A novel, two-step, facile route for the synthesis of pyrrolo[2,3-*b*]quinoxalines via 2,3-dioxopyrroles, enhanced by microwave irradiation, is presented. The newly synthesized 2,3-dioxo-5-halophenyl pyrrolo precursors **4a–c** as well as the non-aromatized ethyl 2-(4-halophenyl)-1-methyl-2,4-dihydro-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **6a–c** and the aromatized ethyl 2-(4-halophenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **7a–c** were evaluated for their antioxidant, cytostatic, and antiviral properties. Most of them proved to be potent hydroxyl radical scavengers and inhibited in vitro lipid peroxidation. The compounds showed moderate antiproliferative activity, while **6a** inhibited vaccinia virus at an EC_{50} value of 2 μM, and **4c** and **6c** inhibited Sindbis virus at EC_{50} values of 4 μM.

Microwave (MW) technology and multicomponent reactions (MCRs) have attracted significant attention from synthetic organic chemists as they accelerate a wide variety of chemical transformations. MWs impart many chemical reactions with attributes such as enhanced reaction rates, higher yields of pure products, better selectivity, improved ease of manipulation, rapid optimization of reactions, and several ecofriendly advantages,[1,2] while MCRs are extremely useful tools for the synthesis of diverse and complex compounds, as well as small and drug-like heterocycles.[3,4] According to current synthetic requirements, environmentally benign multicomponent procedures employing microwave methodology are particularly welcome.

Among various classes of heterocyclic compounds, pyrrolyl[5–7] and quinoxalinyl[8,9] derivatives are well known as antioxidants, presenting potent lipid peroxidation inhibition in vitro and significant hydroxyl radical scavenging activity. The quinoxaline nucleus is present in many pharmaceutical agents exhibiting a broad spectrum of biological activities, such as antitumor, antiviral, antiglaucoma, antitubercular, and anti-inflammatory.[10–13] 2-Oxopyrroles are important substructures in a variety of drugs, including those active against viral infections (HIV,[14] influenza,[15] cytomegalovirus[16]), microbiological diseases[17,18] (bacterial or fungal), and cancer.[19] Finally, pyrroloquinoxaline derivatives[20] are also known as anti-HIV,[21] antimalarial,[22] antagonist,[23] anticancer,[24–26] and antioxidant[27]agents, as well as PARP-1[28] and Akt kinase[29] inhibitors.

Based on the pharmacological interest in compounds that belong to the pyrrolo and quinoxaline families, and considering that only a few methods have been reported for the synthesis of pyrrolo[2,3-*b*]quinoxalines,[27,30–32] we present herein a novel two-step process for the synthesis of 4-chloro, 4-fluoro, and 4-iodophenyl pyrrolo[2,3-*b*]quinoxalines via 2,3-dioxo-pyrroles using microwave irradiation, and a comparison of this methodology with conventional heating.

Our approach to the key intermediates, 2,3-dioxo-5-(4-halophenyl) pyrroles **4a–c**, involved the operationally simple, practical, and economical, three-component condensation of sodium

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diethyl oxalacetate (**3**) with an equimolar amount of an aromatic aldehyde (**1a–c**) and methylamine (**2**), in refluxing ethanol.[33] This reaction provided the desired pyrroles **4a–c** in a one-pot reaction and in moderate yields (36–48%), depending on the halogen on the aromatic aldehyde used (Scheme 1). All the products could be easily filtered from the reaction mixture and could be prepared on multigram scale.

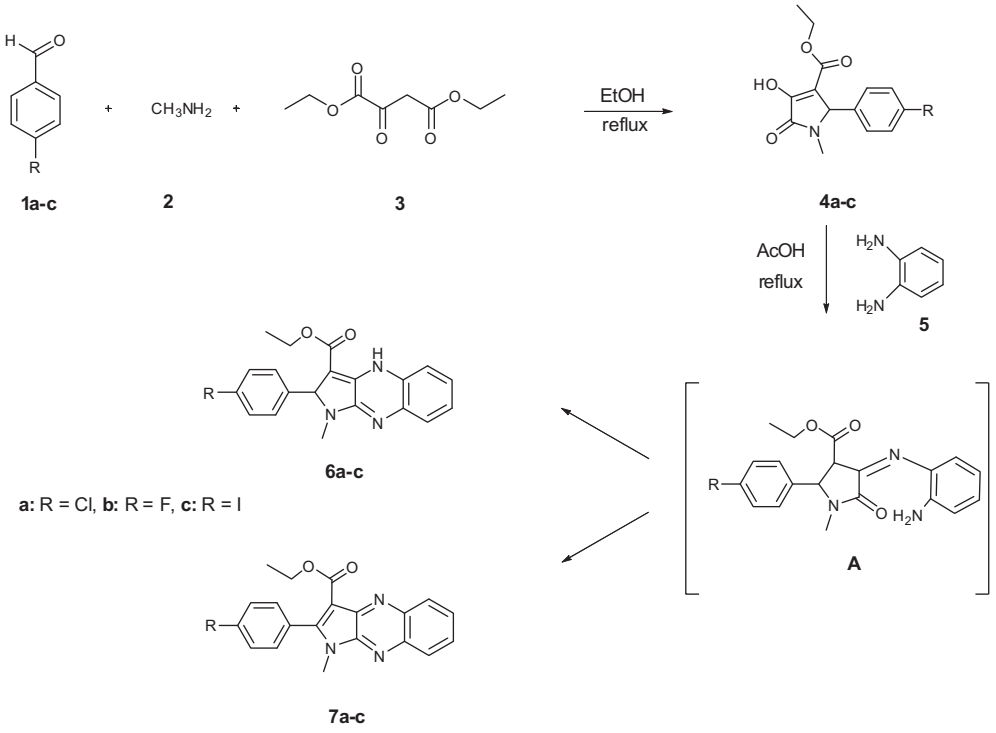
These substituted pyrroles are useful intermediates for the synthesis of pyrrolo[2,3-*b*]quinoxalines **6a–c** and **7a–c**. Therefore, pyrroles **4a–c** were condensed with *o*-phenylenediamine (**5**) in refluxing glacial acetic acid for one hour to give a mixture of two products, which were separable by thin-layer chromatography. The slower moving derivatives were isolated in 39–46% yields and were identified as the non-aromatized ethyl 2-(4-halophenyl)-1-methyl-2,4-dihydro-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **6a–c**, while the less polar analogues corresponding to the aromatized ethyl 2-(4-halophenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **7a–c**, were obtained in slightly higher yields (50–58%) (Scheme 1). When the condensation reaction was performed for two hours, the aromatized isomers **7a–c** were afforded exclusively (65–72%). When oxygen or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used, the starting materials were recovered together with some degradation products. It should be noted that the nature of the halogen on the aromatic ring at position 5 of the heterocycle, in compounds **4a–c**, did not affect the reaction course.

A possible reaction mechanism probably includes an imine–enamine exchange (intermediate A, Scheme 1), which may lead to a favorable situation for the second step (cyclization) to operate; this can directly result from the hydrogen atom on the nitrogen leading to compounds **6**, or from the hydrogen atom on the carbon after cyclic hemiaminal formation leading to compounds **7**.

Since thermally driven organic transformations take place either by conventional heating or microwave accelerated heating, all the reactions were also conducted under MW conditions. Thus, the three-component reaction between aldehydes **1a–c** and methylamine (**2**) with sodium diethyl oxalacetate (**3**) under MW irradiation (100 W) at 110 °C for 20 min produced pyrroles**4a–c**, which were condensed upon irradiation (200 W) with *o*-phenylenediamine (**5**), to afford solely after 3 min at 40 °C the non-aromatized quinoxalines **6a–c** and the aromatized isomers **7a–c** after 10 min at 180 °C (Table 1). When compared to conventional heating, the MW technology completed the two-step synthesis much faster, while the yields of the products were slightly increased (by 4–11%).

All new compounds were characterized by NMR and IR spectroscopy, mass spectrometry, and elemental analysis. Regarding the structures of products **4**, **6**, and **7**, their IR spectra showed the typical absorptions of an α,β-unsaturated ethyl carboxylate at 1625–1698 cm^{-1}. Their ^1H NMR spectra showed signals that could be attributed to the carboethoxy group at 1.00–1.22 ppm (t, 3H) and at 3.97–4.30 ppm (q, 2H). In the ^1H NMR spectra of dihydro analogues **6a–c**, prominent 3-proton methyl signals appeared, which were ascribed to the *N*-methylamino group (**6a**: δ 2.76, **6b**: δ 1.25, **6c**: δ 1.25), while following aromatization the same protons were remarkably deshielded (**7a**: δ 3.78, **7b**: δ 3.78, **7c**: δ 3.77). The ^1H NMR spectra of compounds **6a–c** exhibited signals for the H-2′ protons of the pyrrole ring at 4.85–5.02 ppm as characteristic singlets, contrary to compounds **7a–c**, whose ^1H NMR spectra revealed the absence of such signals.

All the products were evaluated for their antioxidant, cytostatic, and antiviral properties. The interactions of the examined compounds with the 1,1-diphenyl-2-picryl-hydrazyl (DPPH) stable free radical[34] are listed in Table 2, in comparison to the well-known antioxidant agent, nordihydroguaiaretic acid (NDGA). The best DPPH radical scavenging activity was presented by **6b** (at 20 min) and **6a** (at 60 min), while the results for all the analogues at a concentration of 100 μM were time-dependent with the exception of **4c**. A



Scheme 1. Synthesis of the novel 2,3-dioxo-5-(4-halophenyl) pyrroles **4a–c**, ethyl 2-(4-halophenyl)-1-methyl-2,4-dihydro-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **6a–c**, and ethyl 2-(4-halophenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylates **7a–c**.

Table 1
Comparison of conventional and microwave synthetic procedures for the synthesis of compounds **4a–c**, **6a–c**, and **7a–c**

Product	Conventional		Microwave			
	Time (h)	Yield (%)	Time (min)	Yield (%)	Temp (°C)	Power (W)
4a	4	45	20	51	110	100
4b	6	36	20	46	110	100
4c	5	48	20	52	110	100
6a/**7a**	1	46/50	3	56 (only **6a**)	40	200
6b/**7b**	1	42/56	3	53 (only **6b**)	40	200
6c/**7c**	1	39/58	3	50 (only **6c**)	40	200
7a	2	70	10	74	180	200
7b	2	72	10	76	180	200
7c	2	65	10	70	180	200

Table 2
Interaction-reducing activity % with DPPH (RA %); scavenging activity for hydroxyl radicals OH %; % inhibition of lipid peroxidation (AAPH %)

Product	C log *P*[36]	RA % 100 μM 20 min	RA % 100 μM 60 min	OH % 100 μM	AAPH % 100 μM
4a	3.15	13 ± 0.01	15 ± 0.8	No	88 ± 2.1
4b	2.58	22 ± 0.2	41 ± 1.4	No	72 ± 1.7
4c	3.56	42 ± 1.1	21 ± 1.1	No	94 ± 2.9
6a	5.86	41 ± 1.8	65 ± 1.9	92 ± 2.3	90 ± 3.4
6b	4.32	57 ± 1.2	59 ± 0.8	91 ± 3.3	73 ± 2.4
6c	6.27	23 ± 1.1	32 ± 1.0	97 ± 2.7	39 ± 1.9
7a	4.29	23 ± 0.8	26 ± 0.6	No	18 ± 0.5
7b	3.72	6 ± 0.8	22 ± 0.2	95 ± 3.7	59 ± 2.1
7c	4.70	9 ± 0.5	17 ± 0.3	No	No
NDGA[a]	—	81 ± 1.9	83 ± 2.3	—	—
Trolox	—	—	—	73 ± 1.4	63 ± 1.7

[a] NDGA = nordihydroguaiaretic acid; no results under the reported experimental conditions; each experiment was performed at least in triplicate and the standard deviation of absorbance was less than 10% of the mean.

slight increase was observed with **4a**, **6b**, and **7a** after 60 min. When evaluated for their hydroxyl radical scavenging activity generated by the Fe^{3+}/ascorbic acid system, only analogues **6a**, **6b**, **6c**, and **7b** exhibited remarkable activity at 100 μM (being higher than the well-known anti-oxidant, trolox, 73%, Table 2). Among the members of series **7** only **7b**, the F-substituted derivative seemed to be a potent scavenger of hydroxyl radicals, whereas **7a** (Cl-substituted) and **7c** (I-substituted) did not exhibit any activity under the reported experimental conditions. The majority of the studied compounds inhibited effectively 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH)[35]-induced lipid peroxidation at 100 μM, showing higher activity than the reference compound trolox. The results indicated that **4c** with a lipophilicity *c* log *P* value (calculated-theoretical log *P*) of 3.56 presents the highest anti-LPO (lipid peroxidation) ability, whereas **7c** with a higher *c* log *P* value (4.70) shows no activity. Among the derivatives of subgroup **4a–c**, an increase of the overall lipophilicity enhances anti-lipid peroxidation, and particularly enhancement of the lipophilic contribution (π values) of the halogen leads to an increase in the antioxidant activity.

Compounds **4**, **6**, and **7** were also evaluated for their cytostatic activity against murine leukemia L1210, human lymphocyte CEM, and human cervix carcinoma HeLa cells. None of the compounds showed pronounced antiproliferative activity (CC_{50}: $\geqslant$20 μM) with **4c** being an exception that showed cytostatic activity (CC_{50}: 5.8 μM) against HeLa cells, but this compound was markedly less inhibitory against CEM cell proliferation (CC_{50}: 146 μM). The reason for this phenomenon is unclear since the other compounds inhibited tumor cell proliferation at similar potencies irrespective of the nature of the tumor cell-type. The known anticancer compounds, 6-mercaptopurine (6MP) and 6-thioguanine (6TG) were by far superior in their cytostatic activity (CC_{50}: 0.38–2.8 μM) (Table 3) than the test compounds.

When the **4**, **6**, and **7** analogue series were evaluated against a variety of DNA and RNA viruses, none of the compounds proved inhibitory at subtoxic concentrations, except **6a**, which inhibited vaccinia virus-induced cytopathicity at an EC_{50} value of 2 μM (MIC: 100 μM) in HEL cell cultures. This compound may be considered as a potential lead compound for poxvirus inhibition. Compounds **4c** and **6c** showed inhibitory activity against Sindbis virus (EC_{50}: 4 μM).

Table 3
Cytostatic activity of the test compounds

Product	CC_{50}[a] (μM)		
	L1210[b]	CEM[b]	HeLa[b]
4a	274 ± 8	175 ± 6	118 ± 26
4b	119 ± 1	>250	98 ± 5
4c	21 ± 11	146 ± 25	5.8 ± 0.7
6a	43 ± 1	35 ± 2	35 ± 1
6b	93 ± 2	101 ± 11	72 ± 14
6c	51 ± 9	37 ± 1	18 ± 4
7a	216 ± 1	93 ± 28	54 ± 9
7b	176 ± 42	117 ± 51	126 ± 44
7c	34 ± 9	30 ± 19	32 ± 9
6-Mercaptopurine	2.8 ± 1.1	2.8 ± 1.3	1.1 ± 0.1
6-Thioguanine	0.94 ± 0.04	1.1 ± 0.3	0.38 ± 0.17

[a] 50% Cytostatic concentration.
[b] L1210: murine leukemia cells, CEM: human lymphocyte cells, HeLa: human cervix carcinoma cells.

In conclusion, a novel, two-step, facile synthesis of halophenyl pyrrolo[2,3-*b*]quinoxalines enhanced by microwave irradiation has been accomplished via their 2,3-dioxopyrrolo precursors. The reactions occurred remarkably fast under mild conditions using inexpensive reagents, and two types of pyrroloquinoxaline products were isolated based on the amount of time the reactions were heated. Most of the compounds proved to be potent hydroxyl radical scavengers and inhibited in vitro lipid peroxidation. Compounds **6a** and **7b** presented high anti-lipid peroxidation and

hydroxyl radical activity, and compounds **6a**, **4c**, and **6c** showed antiviral activity at subtoxic concentrations, and thus allow us to propose them as templates in the design of antioxidant and antiviral compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.106.

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