Archive for
Organic Chemistry

The Free Internet Journal
for Organic Chemistry

Paper

Arkivoc **2017**, part iv, 315-329

Microwave-assisted synthesis of new imide- and formamide-derivatives of 2(3*H*)-benzoxazolinones and 2(3*H*)-benzothiazolinones

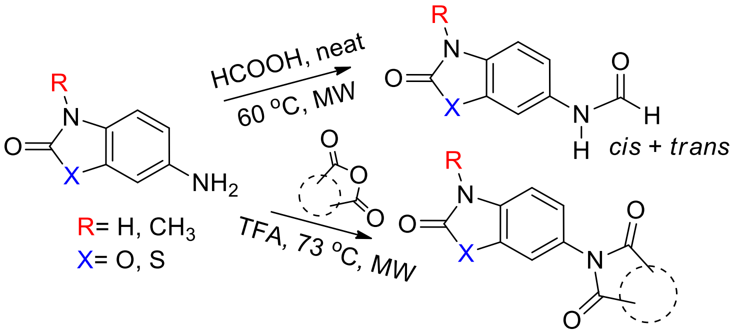
**Khemissi Seddiki,*[a,b,c] Wassila Yahia,[b] Messaoud Liacha,[b] Andrea Defant,[c]
Denise Sighel,[c,d] and Ines Mancini*[c]**

*[a]Laboratoire de Synthèse et Biocatalyse Organique, Faculté des Sciences, Université Badji-Mokhtar de Annaba
B.P. 12, 23000 Annaba, Algérie*
[b] Ecole Préparatoire Aux Sciences Et Techniques, Cité saf-saf BP-218, 23000, Annaba-Algerie
*[c] Laboratorio di Chimica Bioorganica, Dipartimento di Fisica, Università di Trento, via Sommarive 14, 38123
Povo-Trento, Italy*
[d] Centro di Biologia Integrata (CIBIO) Università di Trento, via Sommarive 9, 38123 Povo-Trento, Italy
E-mail: khemissi_seddiki@yahoo.fr

Received 11-04-2016 **Accepted** 05-22-2017 **Published on line** 06-05-2017

Abstract

With the aim to obtain 2(3*H*)-benzoxazolinones and 2(3*H*)-benzothiazolinone derivatives, we synthesized new imide compounds **5a-c**, **6c-d** and **7a-d** by treating their 6-amino precursors with succinic, maleic or phthalic anhydride. The microwave (MW)-assisted reaction provided them more efficiently than through the corresponding isolated amic acids. The same nucleophile reagents were used in a MW-assisted formylation to obtain new formamide products **8-11**, that were detected as cis/trans forms by NMR analysis. The ratio was in favor of the cis isomer and affected by the solvent, as also supported by DFT calculations.



Keywords: Benzoxazolinone, benzothiazolinone, imide derivatives, formamide isomers, DFT calculations

DOI: https://doi.org/10.24820/ark.5550190.p009.926

Introduction

Molecules bearing a 2(3*H*)-benzoxazolinone or 2(3*H*)-benzothiazolinone moiety are considered privileged scaffolds in drug design according to their chemical properties and reactivity.[1] They have shown a high flexibility in chemical modifications, allowing changes on characteristic side-chains anchored to the rigid scaffold, able to provide molecules with interesting therapeutic applications. Several potentially useful compounds based on these pharmacophores were developed, producing molecules with a broad spectrum of bioactivities which include analgesic and anti-inflammatory,[2-4] antioxidant,[5] cytotoxic[6-7] and antinociceptive[8] properties.

Substituted derivatives are reported as scaffolds of non-steroidal anti-inflammatory drugs (NSAID), based on an observed analgesic activity. For example, tiaramide (1-[2-(5-chloro-2-benzothiazolinone3-yl) acetyl]-4-hydroxyethyl piperazine) is a drug that prevents the synthesis of prostaglandins and therefore has a strong anti-inflammatory activity.[9] Quantum chemical calculations were applied to a small library of 6-acylbenzothiazolone derivatives, with the aim to establish a structure–activity relationship useful for the design of new analgesic drugs.[10,11]

Recently, a series of urea and thiourea derivatives of 3-methyl-2(3*H*)-benzothiazolone have been evaluated for antibacterial and antifungal activities.[12] Besides 2(3*H*)-benzoxazolinones and 2(3*H*)-benzothiazolinones with a *N*-methyl group, the corresponding *N*-H heterocycles find a particular interest in medicinal chemistry as precursors of differently N-functionalized analogues.[13]

Procedure where the conventional heating is replaced by microwave (MW) irradiation have been widely applied in organic synthesis, due to its general high efficiency in terms of reduced reaction time and increased product yield, eco-friendly nature by possible solvent-free conditions, and experimental ease of manipulation.[14,15] MW-assisted synthesis is also employed in modern drug discovery often in connection with a multicomponent approach of the target molecules, a remarkable portion of which are heterocycles.[16-18]

The study on formylation of the amine group has attracted attention as a reaction with a biological relevance. It occurs on amino acids and was identified to be involved in the initiation of protein synthesis in bacteria[19] and recently in a histone modification which may modulate gene expression.[20] The isomerism of the amide group is of some interest due to its partial double bond character and has been studied in order to understand protein structure.[21]

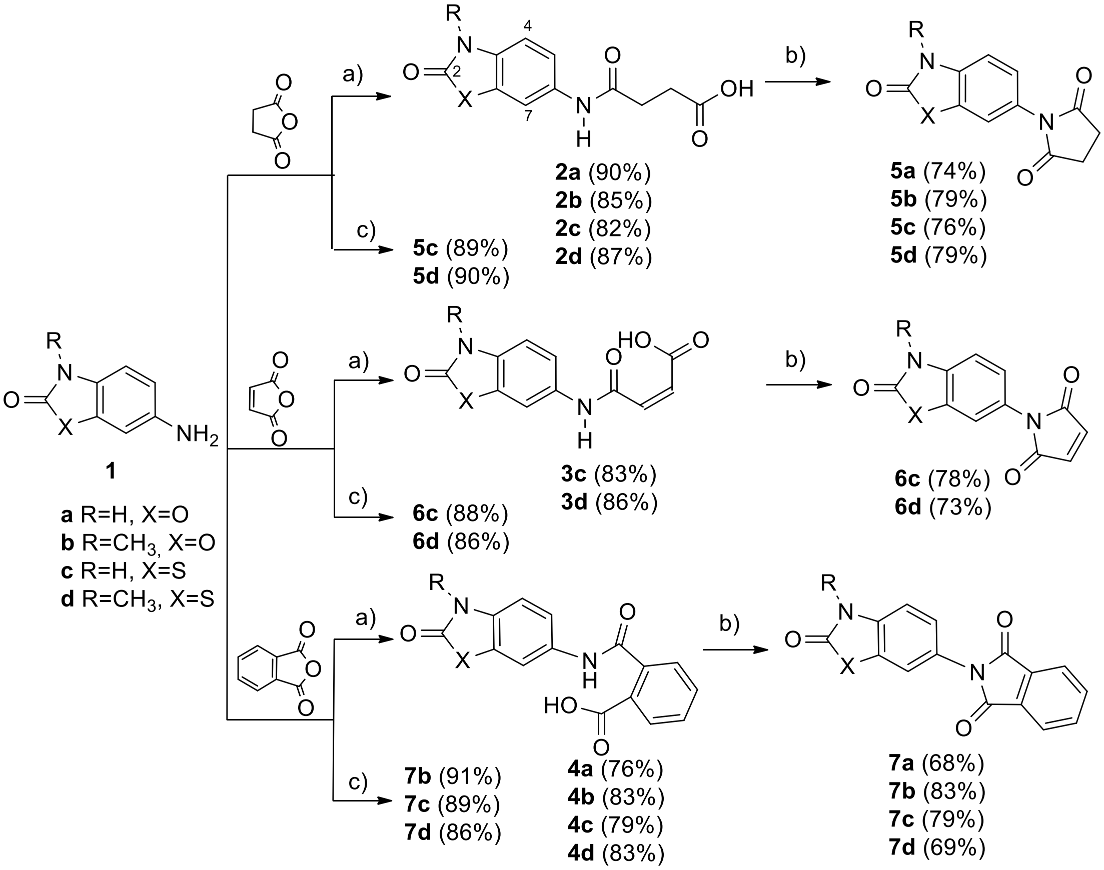
We report here on the MW-assisted synthesis of new 2-benzoxazolinone and 2-benzozathiazolinone derivatives, bearing either a HN(3) or a methyl-N(3) group, and functionalized at the 6-amino group as imide or as formamide. In the latter case, insights into the molecular structures of the isomeric products by a formylation reaction have been taken into account by NMR analysis and density functional theory (DFT) calculation.

Results and Discussion

In the context of bioisosterism, based on the hypothesis that molecules with similar electronic structures tend to exert similar biologic activities, 6-aminobenzoxazolinone and 6-amino-benzothiazolinone are promising precursors for the production of new O/S isosters with potential improved bioactivities. Both 6-amino-2(3*H*)-benzoxazolinone (**1a**) and 6-amino-2(3*H*)-benzothiazolone (**1c**) are commercially available, whereas the *N*-methyl analogues **1b** and **1d** can be obtained starting from 3-methyl-2(3*H*)-benzoxazolone or from the corresponding thia-compound after aromatic nitration with HNO_3/ Ac_2O at 0-5 °C and reduction with $SnCl_2·2H_2O$ under reflux in ethanol according to the reported procedure.[22]

The series of amic acids **2a-d**, **3c-d** and **4a-d** were obtained treating each of the corresponding 6-aminobenzoxazolinones **1a**, **1b** or 6-aminothiazolinones **1c**, **1d** with succinic, maleic or phthalic anhydride in THF at room temperature for 1-2 hours (Scheme 1). After partial solvent concentration, the products were isolated in good yields by precipitation from the reaction mixture and with a good purity as established by NMR and MS analysis. In details, ESI-MS/MS experiments on $[M-H]^-$ ions gave fragments corresponding to the loss of carbon dioxide and water, whereas electron impact MS(EI) spectra showed intense signals due to the loss of water from the corresponding undetectable molecular peak. This fact can be attributed to the production of imide derivatives (reported below) under the high temperature conditions applied in the measurement.

The presence of a carboxylic group on these molecules offers the opportunity to further functionalize them. The benzoxazolinones **2a** has been reported,[23] and both **2b** and **3b** are now commercially available. By heating the amic acids **2a-d**, **3c-d** and **4a-d** at 80 °C for one hour in acetic anhydride with an equimolecular amount of sodium acetate,[24] we have obtained a series of N-arylimide derivatives (**5a-d**, **6c-d** and **7a-d**).

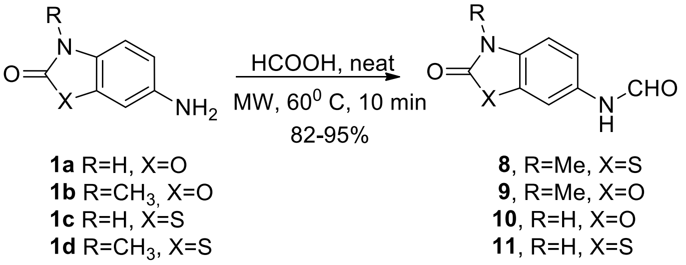


Scheme 1. Synthesis of imides **5a-d, 6a-d** and **7a-d**. Reagents and conditions: a) THF, rt, 1-2 h. b) CH_3COONa, Ac_2O, 80 °C, 1 h. c) MW irradiation, TFA, 73 °C, 15 min. Arbitrary numbering is for convenience.

MW irradiation of the 6-amino aryl reagent **1a-d** with the suitable anhydride in TFA at 73 °C for 15 minutes provided the corresponding imide products in higher yields if compared with the two-step conventional method. In detail, by a single step and shorter reaction time, starting from **1c-d**, the imides **5c-d** were obtained by reaction with succinic anhydride, **6c-d** by reaction with maleic anhydride and **7b-d** by reaction with phthalic anhydride (Scheme 1). The products were isolated in solid form and were structurally characterized by NMR analysis and mass spectrometry (Experimental Section).

This one-pot production of N-arylimide derivatives is less time-consuming and more efficient since it gives higher yields (86-91%) compared to the two-step method where the amic acids obtained at room temperature are subsequently cyclized upon conventional heating, with global yields in the range 57-69% starting from **1a-d** (Scheme 1).

6-Amino-3-methyl-2(3H)-benzothiazolinone (**1d**), 6-amino-3-methyl-2(3H)-benzoxazolinone (**1b**) and the demethylamines **1a** and **1c** were also used as nucleophilic reagents with formic acid in MW-assisted reactions at 60°C for 10 minutes, to give the corresponding new formamide derivatives **8-11** in high yields (Scheme 2).



Scheme 2. Microwave-assisted synthesis of formamide derivatives **8-11**.

^{1}HNMR spectrum of compound **8** in $CDCl_3$ shows the presence of two related molecules, in particular we found pairs of signals as doublets centered at δ 8.57 (*J* 11.6 Hz) and δ 8.37 (*J* 1.6 Hz) for the formyl proton, broad singlets at δ 7.70 and δ 7.21 for the NH amide proton and singlets at δ 3.45 and δ 3.43, all these in a 1: 2 ratio, respectively. The phenomenon is due to the partial single-double bond feature of the H*N*-CHO amide bond that restricts the rotation around this bond so that the cis and trans forms are both possible when referring to the relative position of formyl and secondary amide hydrogen atoms,which correspond to Z and E isomers, respectively.

The coupling constant values 11.6 and 1.6 Hz for the formyl protons allow the assignments of the signals to the trans and cis isomers, respectively. This result is in agreement with reported data for N-methylformamide and N-phenylformamide,[25] as well as for N-formyl-o-toluidine and a series of strictly related N-monoalkylsubstituted formamides.[26]

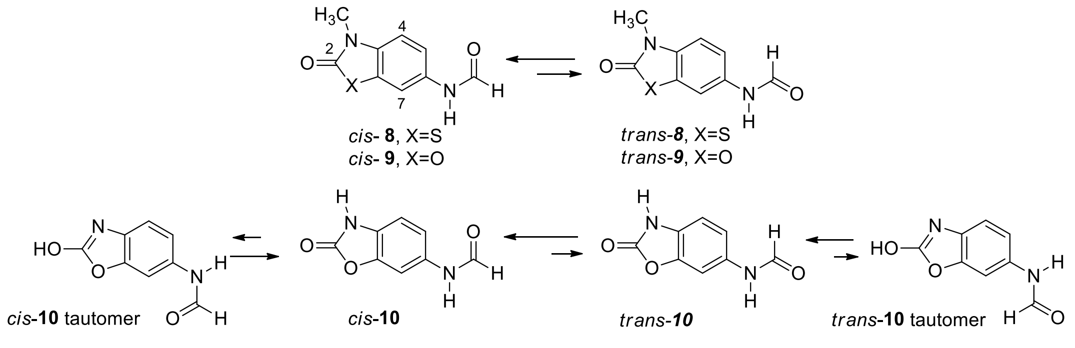


Figure 1. Isomeric forms of formamide derivatives **8-10.**

Further support to these assignments comes from the resonance of the trans-C(O)H proton at lower fields than for the cis form, attributable to the closer proximity of the trans -C(O)H proton to the phenyl ring that produces a larger ring-current.[23] The downfield shifts for H-5 (δ 7.37) and H-7 (δ 7.84) protons observed in trans form compared with the signals (δ 7.06 and 7.20, respectively) for the cis isomer are also in agreement with the behavior of the corresponding aromatic proton in *ortho*-position reported for cis/trans forms of *N*-formyl-o-toluidine.[26]

It was also observed that the amide NH signals shifted depending on the concentration of **8** in $CDCl_3$ solution, so that the detectable signals at δ 7.70 for the cis (br d, *J* 11.6 Hz) and at δ 7.31 (br s) for the trans isomers moved to δ 7.76 and 7.83 respectively in an about four times more concentrated solution. This solvent effect is compatible with the increase of solute-solute hydrogen bonding in more concentrated solutions.[25] Neither shifts for HC(O) proton nor isomer ratio change was instead observed upon dilution or concentration of the solution.

The isomeric ratio resulted sensitive to the type of solvent used for the NMR analysis, in fact, replacing $CDCl_3$ with CD_3OD, the trans/cis ratio moved to 1:5, with the cis form predominant also in this case(Table 1). We could attribute the signalsat δ 8.25 and δ 8.64 to the trans and cis forms respectively, assuming also here the aforementioned downfield shift of the trans-formyl proton due to the closer proximity to the phenyl group. This assignment finds a support in DFT-minimized structures, where the 2.23 Å distance was evaluated between H-5 and amide oxygen. In addition, as expected, the signal for HC(O) protons became singlets due to the H/D exchange on NH position. The presence of trans/cis forms is also confirmed by the doubling of the signals for all the carbon atoms observed in ^{13}C NMR spectra. In details, the values for the trans isomer are at lowerfields if compared to those corresponding to the cis isomer, which are in a higher proportion, in agreement with reported data.[26]Similar results were found for the 3-methyl benzoxazolylformamide **9** (Exper. Section).

Due to the poor $CDCl_3$ solubility observed for the more polar products **10** and **11**, their NMR spectra were recorded in CD_3OD. Also for these compounds the presence of two forms was shown, with the CHO signals as singlets at δ 8.26 and 8.62 in 5:2 ratio for **10** and at δ 8.24 and 8.61 in 4:1 ratio for **11**, attributable to each cis/ trans pair respectively, based on the downfield position of doublet for the minor trans isomer in $CDCl_3$ spectra of **8** and **9**. In addition, the cis form resulted the major one also in DMSO-d_6, where the 3:1 cis/trans ratio evaluated for **11** was based on the relative intensities of the corresponding CHO signals at δ 8.23 as a broad singlet and at δ 8.63 as a doublet (*J* 11.5 Hz), (Table 1).

Table 1.^{1}HNMR (400 MHz) signals for the formyl proton in compounds **8**-**11**

	HC(=O)N (δ in ppm, *J* in Hz)			
Compound	Solvent	cis	trans	cis/trans ratio
8	$CDCl_3$	8.37 (d,1.6)	8.55 (d,11.6)	2:1
9	$CDCl_3$	8.37 (d,1.6)	8.55 (d,11.6)	2:1
8	CD_3OD	8.25 (br s)	8.63 (br s)	5:1
9	CD_3OD	8.25 (br s)	8.63 (br s)	5:1
10	CD_3OD	8.25 (br s)	8.62 (br s)	5:2
11	CD_3OD	8.24 (br s)	8.61 (br s)	4:1
11	DMSO-d_6	8.23 (br s)	8.63 (d,11.5)	3:1

A confirmation to these data came from energy-minimized structures obtained by DFT calculation. Phenyl and substituted-phenylformamides have been studied as simple models for peptide-like configurations[27,28] with different basis sets tested in the investigation of small model amide, e.g. *N*-methylamide. The efficacy of the methods was reported comparing the calculated amide frequencies with those measured in solution by IR spectroscopy. This allowed to select BPW91 hybrid functional with a small basis set as the best method to predict the amide frequencies both in gas-phase and in solution with a good approximation.[29,30] In our hands, DFT (BPW91) method also resulted the best approach when applied to arylformamides **8-11**, with 6-31G (d,p) as the basis set of choice for all atoms, except for sulfur atom in molecules **8** and **11**, where 6-311+(3df,p) basis set was used. Energy-minimized structures for the isomeric forms of compound **8** display lengths of 1.37 Å for N-CO and 1.23 Å for C=O bonds. The cis isomer presents a full planar disposition, whereas the trans isomer presents a dihedral angle of 31.9° between the plane containing the aryl group and the one containing the formyl unit (Figure 2). A similar behavior has been also observed for the cis/trans forms of **9-11**, where the cis isomer always displays a planar structure.

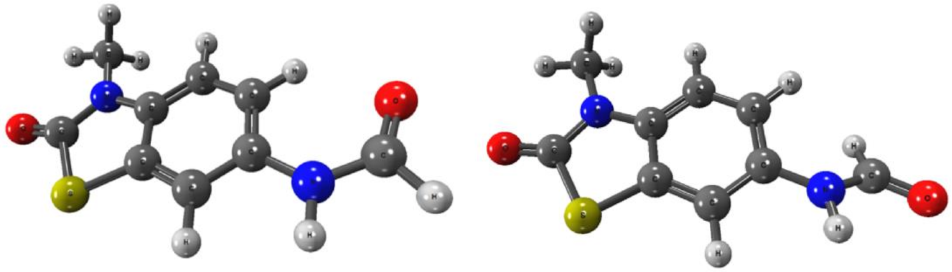


Figure 2. Energy-minimized structures of *cis* (left) and *trans*(right) forms for formamide **8**, calculated at the BPW91/6-31G (d,p) level of theory in methanol solution.

The calculated energy values obtained for the minimized structure of formamide **8** in chloroform solution confirmed that the cis form is more stable than the trans, in agreement with the 2:1 ratio observed in $CDCl_3$ by ^{1}H NMR spectrum. Besides this, the highest amount of the cis over the trans form observed in ^{1}HNMR spectra recorded for each formamide **8**-**11** in CD_3OD can be correlated to their higher stability, as established by DFT calculation in methanol solutions(Table 2).

The N(3)-demethyl products **10** and **11** present the possibility of different tautomeric forms, among which the most probable are the 2-hydroxybenzoxazolyl and 2-hydroxybenzthiazolyl ones (Figure 1). For the four isomers taken into account in DFT calculation for molecules **10** and **11**, the cis form of the 2-oxo tautomer resulted the most stable (Table 2). In addition the high energy values obtained for the cis and trans 2-hydroxytautomers are in line with the not appreciable presence of the corresponding signals in NMR spectra.

Table 2. Data by DFT calculation at the level of theory BPW91/6-31G (d,p) for formamides **8-11**, added of BPW91/6-311+(3df,p) for sulfur atom in **8** and **11**: relative energy values for the trans-minimized structures with respect to the corresponding cis-form (taken as reference =0 KJ/mol) and dihedral angles (in degrees) between the aromatic and formamide units, in the indicated solvents.

Compound	in $CHCl_3$		in MeOH	
	cis	trans	cis	trans
	Energy (KJ/mol)			
8	0	16.32	0	38.91
9	0	5.65	0	5.31
10	0	5.44	0	5.73
10 taut	64.43	71.13	66.53	73.64
11	--	--	0	6.01
11taut	--	--	66.02	71.57
	Dihedral Angle			
8	0	-35.02	0	-34.11
9	0	-34.60	0	-33.96
10	0	-33.99	0	-33.54
10 taut	0	-30.63	0	-30.39
11	--	--	0	-31.73
11 taut	--	--	0	-30.09

Conclusions

6-Amino functionalized 2(3*H*)-benzoxazolinones and 2(3*H*)-benzothiazolinones and their *N*(3)-methyl derivatives have been converted into the corresponding imide derivatives upon treatment with succinic, maleic or phthalic anhydrides by one-pot MW-assisted reactions. This procedure is more efficient compared with the two-step method where the amic acids are produced at room temperature and subsequently cyclized upon conventional heating. The same aryl amines were also employed as nucleophilic reagents in a MW-assisted formylation to give the corresponding formamide derivatives. We investigated the cis/trans ratio of these products by both NMR analysis (under different concentration and solvent conditions) and by considering their minimized energy structures obtained by DFT calculations.

Experimental Section

General. Melting points were determined using a Reichert Thermovar apparatus. Infrared spectra were recorded by using a FT-IR Tensor 27 Bruker spectrometer equipped with an Attenuated Transmitter Reflection (ATR) device at 1 cm^{-1} resolution in the absorption region $\Delta\nu$ 4000–1000 cm^{-1}. A thin solid layer was obtained by evaporation of the methanol solution of the sample. The instrument was purged with a constant dry nitrogen flow. Spectral processing was made using the Opus software package. NMR spectra were recorded by an Avance 400 Bruker spectrometer: ^1H at 400 MHz and ^{13}C at 100 MHz in $CDCl_3$ or CD_3OD; δ values are reported in ppm relative to the solvent residual signals $\delta_H = 7.25$ and $\delta_C = 77.00$ ppm for $CDCl_3$, $\delta_H = 3.31$ and $\delta_C = 49.00$ for CD_3OD, $\delta_H = 2.49$ and $\delta_C = 39.50$ ppm for DMSO-d_6 relative to $SiMe_4$ (=0 ppm); *J* values in Hertz. Assignments are supported by heteronuclear single quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC) experiments. Electron impact (EI) mass spectra (*m/z*; rel.%) and high-resolution EI data performed on a Kratos-MS80 mass spectrometer with a home-built computerized acquisition software. Electrospray ionization (ESI)-MS mass spectra and tandem fragmentation spectra (MS/MS) were taken with a Bruker Esquire-LC spectrometer equipped with an electrospray ion source used in positive or negative ion mode by direct infusion of a methanolic solution of the sample, under the following conditions: source temperature 300 °C, drying gas N_2, 4 $Lmin^{-1}$, scan range *m/z* 100–1,000.High-resolution ESI MS measurements for compounds **2**-**4** were obtained by direct infusion using an Orbitrap Fusion Tribrid® mass spectrometer. Solvents and reagents were purchased from Sigma Aldrich Europe or Alfa Aesar and were used without purification. Thin-layer chromatography (TLC) was carried out on Merck Kieselgel Si60 PF254 and spots visualized at 254 nm. Preparative TLC (PLC) was realized on 20 × 20 cm Merck Kieselgel 60 F254 0.5 mm plates. MW-assisted reactions were carried out using a mono-mode CEM Discover reactor in a sealed vessel, monitoring the temperature of reaction mixtures by an external infrared control system. All evaporations were carried out at reduced pressure. Products **2a-2d**, **3c**-**3d**, **4a-4d** were recrystallized from methanol and imides **5a-5d**, **6c**,**6d** and **7a-7d** from hexane/ethyl acetate before carrying out analysis for structural characterization.

Computational details. Starting structures were generated by molecular mechanics minimization, using PC Model (Serena Software, version 7.00). Quantum chemical calculations were performed using the Gaussian 03W revision E.01 package program set.[31] The 6-31G (d,p) was the standard basis set of choice for all atoms of the first and second row, whereas 6-311+(3df,p) basis set was used for sulfur atom. The gradient-corrected DFT was BPW91 method which uses the GGA (Generalized Gradient Approximation) exchange functional of Becke[32] and the PW91 GGA correlation functional of Perdew and Wang.[33] The functional was parameterized using the Monte Carlo results of Ceperley and Alder.[34] Perdew and Wang considered all the Ceperley and Alder data, including the uncertainty in each data point. They fit the functional to match the correct low-density behavior for the correlation.[33] The simulations were made in the presence of methanol or chloroform using the polarizable continuum model (PCM). The optimized structural parameters were employed in the vibrational energy calculations at the DFT levels to characterize all stationary points as minima. For each optimized structure, no imaginary wavenumber modes were obtained, proving that a local minimum on the potential energy surface was actually found.

General procedure for the synthesis of amic acids 2a-d, 3c-d and 4a-d, exemplified by 4-oxo-4-((2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)amino)butanoic acid (2a). A solution of anhydride (23.5 mg, 0.240 mmol) was treated with arylamine **1a** (32.6 mg, 0.240 mmol) in anhydrous THF (1 mL) and the reaction mixture was stirred at room temperature for 1-2 hours. The progress of the reaction was monitored by TLC (ethyl acetate/hexane 6:4 v/v). Once the reaction was completed, the solvent was evaporated under reduced pressure to obtain the corresponding solid amic acids (53.9 mg, yield: 90%).

4-Oxo-4-((2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)amino)butanoic acid (2a).[23] White solid, mp 142-143 °C. ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.60 (1H,d, *J* 2.0 Hz, H-7), 7.21 (1H, dd, *J* 8.4, 2.0 Hz, H-5), 6.98(1H,d, *J* 8.4 Hz, H-4), 2.65(4H, s, CH_2-CH_2). EIMS: *m/z* 232 ($[M^{+\cdot}-H_2O]$, 100), 250 (33).ESIMS(+): *m/z* 273($[M+Na]^+$); MS/MS (273): *m/z* 173; ESIMS(-): *m/z* 249($[M-H]^-$); MS/MS (249): *m/z* 149.

4-((3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)amino)-4-oxobutanoic acid (2b). Also commercially available. White solid, yield: 85%, mp 135-136 °C. ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.62(1 H, d, *J* 2.0 Hz, H-7), 7.20(1H, dd, *J* 8.4, 2.0 Hz, H-5), 6.98 (1H, d, *J* 8.4 Hz, H-4), 3.40(3H, s, CH_3-*N*), 2.66 (4H, s, CH_2-CH_2). EIMS: *m/z* 246 ($[M^{+\cdot}-H_2O]$, 94).ESIMS(-): *m/z* 263($[M-H]^-$); MS/MS (263): *m/z* 245.

4-Oxo-4-((2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)amino)butanoic acid (2c). Purple solid, yield: 82%, mp 151-152 °C. ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.76(1H, d, *J* 2.0 Hz, H-7), 7.34(1H,dd, *J* 6.4, 2.4 Hz, H-5), 7.05(1H, d, *J* 8.4 Hz, H-4), 2.65(4H, br s, CH_2-CH_2). ^{13}CNMR (CD_3OD, detectable by HMBC):δ_C176.3, 172.8, 123.3, 120.2, 119.5, 32.30, 30.0. EIMS: *m/z* 248 ($[M^{+\cdot}-H_2O]$, 88).ESIMS(-): *m/z* 265($[M-H]^-$), MS/MS (265): *m/z* 247, 22, 165; ESIMS(+): *m/z* 289($[M+Na]^+$); MS/MS (289): *m/z* 189. HRMS(ESI-) $[M-H]^-$: 279.02632±0.00500 ($C_{12}H_{11}N_2O_4S$, calcd 279.04450).

4-((3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)amino)-4-oxobutanoic acid (2d). Solid, yield: 87%, mp 133-134 °C. ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.84(1H, d, *J* 2.0 Hz, H-7), 7.45(1H, dd, *J* 8.8, 2.0 Hz, H-5), 7.16(1H, d, *J* 8.8 Hz, H-4), 3.43(3H,s, *N*CH_3), 2.66(4H, brs, CH_2-CH_2). ^{13}C NMR (100 MHz, CD_3OD): δ_C170.3, 164.9, 134.9, 134.1, 133.9, 122.5, 124.8, 118.3, 32.1, 30.4, 28.1. EIMS: *m/z* 262 ($[M^{+\cdot}-H_2O]$, 82). ESI(-)-MS: *m/z*279($[M-H]^-$), MS/MS (279): *m/z* 261; ESIMS(+): *m/z* 303($[M+Na]^+$); MS/MS (303): *m/z* 203. HRMS(ESI-) $[M-H]^-$: 279.02632±0.00500($C_{12}H_{11}N_2O_4S$, calcd 279.04450).

(*E*)-4-Oxo-4-((2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)amino)but-2-enoic acid (3c). Yellow solid, yield 83%, mp 137-138 °C. ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.87(1H, d, *J* 2.0, H-7), 7.43(1H, dd, *J* 6.8, 2.0 Hz, H-5), 7.10 (1H, d, *J* 6.8 Hz, H-4), 6.55 and 6.31(two d, 1H each, *J* 12.4 Hz, CH=CH). ^{13}CNMR (100 MHz, CD_3OD): 168.4, 167.1, 133.4, 132.7, 130.5, 128.5, 123.0, 122.4, 118.8. EIMS: *m/z* 246 ($[M^{+\cdot}-H_2O]$, 32).ESI(-)-MS: *m/z* 263($[M-H]^-$), MS/MS (263): *m/z* 245, 219; ESIMS(+): *m/z* 287($[M+Na]^+$). HRMS(ESI-) $[M-H]^-$: 263.01042±0.00500 ($C_{11}H_7N_2O_4S$, calcd 263.01320).

(*E*)-4-((3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)amino)-4-oxobut-2-enoic acid (3d). Yellow solid, yield: 86%, mp 111-112 °C. ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.94(1H, d, *J* 2.0 Hz, H-7), 7.53(1H, dd, *J* 6.8, 2.0 Hz, H-5), 7.22(1H, d, *J* 8.4 Hz, H-4), 6.56 and 6.31 (two d, 1H each, *J* 12.4 Hz, CH=CH, 3.44(s, 3H, *N*CH_3). ^{13}CNMR (100 MHz, DMSO-d_6):δ_C168.4, 166.7, 163.1, 134.2, 133.90, 131.5, 131.4, 130.5, 121.6, 118.4, 29.0. EIMS: *m/z* 260 ($[M^{+\cdot}-H_2O]$, 72), 231 (32).ESI(-)-MS: *m/z* 277($[M-H]^-$), MS/MS (277): *m/z* 233; ESIMS(+): *m/z* 301($[M+ Na]^+$), 279 ($[M+H]^+$); MS/MS (279): *m/z* 261, 181.HRMS(ESI-)$[M-H]^-$: 277.02834±0.00500 ($C_{12}H_9N_2O_4S$, calcd 277.02885).

2-((2-Oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)carbamoyl)benzoic acid (4a). White solid, yield: 76%, mp 203-204 °C. ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.03(1H, d, *J* 8.1 Hz, aryl), 7.72(1H, d, *J* 1.8 Hz, H-7), 7.66(1H, d, *J* 8.1 Hz, aryl), 7.58(2H, m, aryl), 7.32(1H, dd, *J* 8.4, 1.8 Hz, H-5), 7.05(1H, d, *J* 8.4 Hz, H-4). ^{13}C NMR (100 MHz, CD_3OD): δ_C 170.9, 140.0, 135.1, 133.2, 132.2., 130.9, 128.5, 117.6, 110.4. EIMS: *m/z* 280 ($[M^{+\cdot}-H_2O]$, 98), 236 (8). ESIMS(-): *m/z* 297($[M-H]^-$); MS/MS (297): *m/z* 253.HRMS(ESI-) $[M-H]^-$: 297.05078±0.00500($C_{15}H_9N_2O_5$, calcd 297.051695).

2-((3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)carbamoyl)benzoic acid (4b). White solid, yield: 83%, mp 195-196 °C.^{1}H NMR (400 MHz, CD_3OD): δ_H 8.01(1H, d, *J* 7.8 Hz, aryl), 7.75(1H, d, *J* 1.6 Hz, H-7), 7.69(1H, d, *J* 7.8

Hz, aryl), 7.56(2H, m, aryl), 7.38(1H, dd, *J* 8.6, 1.6 Hz, H-5), 7.11(1H, d, *J* 8.6 Hz, H-4), 3.39(s, 3H, NCH_3). ^{13}C NMR (100 MHz, CD_3OD): 167.1, 162.5, 134.5, 131.7, 131.5, 123.6, 123.4, 118.1, 28.2. EIMS *m/z*(%): 294([$M^{+\cdot}$-H_2O], 32).ESIMS(+): *m/z* 335([M+Na]$^+$); ESIMS(-): *m/z* 311([M-H]$^-$); MS/MS (311): *m/z* 267. HRMS(ESI-) [M-H]$^-$: 311.06541±0.00500 ($C_{16}H_{11}N_2O_5$,calcd 311.06735).

2-((2-Oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)carbamoyl)benzoic acid (4c). White solid, yield: 79%, mp 232-233 °C.^{1}H NMR (400 MHz, CD_3OD): δ_H 8.02(1H, d, *J* 7.8 Hz, aryl), 7.86(1H, d, *J* 1.7 Hz, H-7), 7.65(1H, d, *J* 7.8 Hz, aryl), 7.56(2H, m, aryl), 7.45(1H, dd, *J* 8.6, 1.7 Hz, H-5), 7.10 (1H, d, *J* 8.6 Hz, H-4). ^{13}CNMR (100 MHz, CD_3OD): δ_C173.5, 171.6, 134.5, 132.4, 132.1, 130.9, 128.3, 123.2, 122.3.EIMS: *m/z* 296 ([$M^{+\cdot}$-H_2O], 82), 298(5). ESIMS(-): *m/z* 313([M-H]$^-$), MS/MS (313): *m/z* 295, 269.HRMS(ESI-) [M-H]$^-$: 313.03065±0.00500 ($C_{15}H_9N_2O_4S$, calcd 313.02885).

2-((3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)carbamoyl)benzoic acid (4d). White solid, yield: 83%, mp 195-196 °C.^{1}H NMR (400 MHz, CD_3OD):δ_H 8.04(1H, d, *J* 7.8 Hz, aryl), 7.95(1H, br s, H-7), 7.64 (1H, brd, *J* 8.0Hz, H-5), 7.56(2H, m, aryl), 3.45(3H, s, *N*CH_3). 7.21 (1H, d, *J* 8.0Hz, H-4).^{13}CNMR (100 MHz, $CDCl_3$):δ_C169.8, 167.2, 134.6, 131.8, 131.6, 125.0, 123.9, 121.1, 118.1, 29.2. EIMS *m/z*(%): 310(([$M^{+\cdot}$-H_2O], 84). ESIMS(-): *m/z* 327([M-H]$^-$), MS/MS (327): *m/z* 283.HRMS(ESI-) [M-H]$^-$: 327.04882±0.00500($C_{16}H_{11}N_2O_4S$, calcd327.04450).

General procedure for the synthesis of imides 5a-d, 6c-d and 7a-d from the corresponding amic acids, exemplified by 1-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)pyrrolidine-2,5-dione (5a). Compounds **2a** (45 mg, 0.180 mmol) was heated in acetic anhydride (0.75 mL) with sodium acetate (14.7 mg, 0.180 mmol) at 80 °C for one hour. The progress of the reaction was monitored by TLC (ethyl acetate: hexane 6:4). Once the reaction was completed, the mixture was cooled at room temperature, poured into ice cold water, the precipitate was filtered off and dried to obtain solid products (27.5 mg, 66%). Alternatively, the reaction mixture was poured into ice cold water, extracted with dichloromethane (25 mL x3), the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The second work up provided higher yields of products (30.8 mg, 74%), detected as a single UV spot in TLC (ethyl acetate: hexane 6:4).

1-(2-Oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)pyrrolidine-2,5-dione (5a). White solid, yield: 74%, mp 163-164 °C. IR (neat) ν_{max}1819s, 1702 vs, 1630w, 1491s, 1446w, 1401m, 1371w, 1308vs, 1274m, 1252m, 1184vs, 1160s, 1128w, 1021vs, 921w, 878m, 844m, 828m, 809w, 754m, 677s,cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.15(1H, d, *J* 8.4 Hz, H-4), 7.23(1H, dd, *J* 8.4, 2.0 Hz, H-5), 7.21(1H, d, *J* 2.0 Hz, H-7), 2.90(4H,s, CH_2-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$):δ_C 175.68(2C), 151.18, 142.20, 129.01, 127.52, 123.19, 108.82, 28.34 (2C). ESIMS(-): *m/z* 231([M-H]$^-$); EIMS: *m/z* 232 ($M^{+\cdot}$, 100), 150(24), 81(18); HRMS(EI): 232.04789 ±0.0020 ($C_{11}H_8N_2O_4$, calcd 232.04841).

1-(3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)pyrrolidine-2,5-dione (5b). White solid, yield: 79%, mp 172-173 °C. IR (neat) ν_{max} 1771vs, 1755vs, 1697vs, 1621w, 1503m, 1406m, 1378m, 1359m, 1292w, 1274w, 1249w, 1221w, 1183vs, 1148w, 1132w, 1093w, 1055m, 1014w, 977w, 936m, 874m, 824s, 747m, 710w, 671vs cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.13(1H, d, *J* 1.2 Hz, H-7), 7.21(1H, dd, *J* 8.0, 1.2 Hz, H-5), 8.15(1H, d, *J* 8.0 Hz, H-4), 2.98 (4H, s, CH_2-CH_2). 2.75(3H,s, *N*CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C175.98(2C), 154.54, 142.56, 131.92, 126.51, 122.56, 109.11, 108.02, 29.68, 28.35(2C). Significant long range correlations (HMBC): δ_H 2.98 with δ_C175.98(CON), δ_H2.75with δ_C126.51(C3a). EIMS *m/z*(%):246($M^{+\cdot}$,65), 190(16), 164(42), 98(8); HRMS(EI): 246.06363±0.0020 ($C_{12}H_{10}N_2O_4$, calcd. 246.06406).

1-(2-Oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)pyrrolidine-2,5-dione (5c). Yellow solid, yield: 76%, mp 159-160 °C, IR (neat) ν_{max}1697vs, 1490m, 1409w, 1392w, 1279w, 1181s, 1008w, 873w, 821m, 725m, 650s, cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.42(1H, d, *J* 8.6 Hz, H-4), 7.37(1H, d, *J* 2.0 Hz, H-7), 7.30(1H,dd, *J* 8.6, 2.0 Hz, H-5), 2.90(4H, s, CH_2-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 175.63 (2C), 170.62, 134.38, 129.22, 125.13, 122.66, 119.89, 118.32, 28.35(2C). ESIMS(-): *m/z* 247([M-H]$^-$); MS/MS (247): *m/z* 203, 191. EIMS: *m/z* 248 ([$M^{+\cdot}$,100). HRMS(EI): 248.02426±0.0020 ($C_{11}H_8N_2O_3S$, calcd. 248.02556).

1-(3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)pyrrolidine-2,5-dione (5d). Yellow solid, yield: 79%, mp 135-136 °C, IR (neat) ν_{max}1773w, 1702s, 1672vs, 1586w, 1492m, 1393w, 1351w, 1324w, 1292w, 1261w, 1242w, 1180vs,1136w, 1048w, 1012w, 877w, 827w, 805m, 773w, 722w, 703w, 665m, 645m, 608m, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.38(1H, d, *J* 2.0 Hz, H-7), 7.26(1H, dd, *J* 8.5, 2.0 Hz, H-5), 7.10(1H, d, *J* 8.5 Hz, H-4), 3.43(3H,s, *N*CH_3), 2.91(4H, s, CH_2-CH_2).^{13}C NMR (100 MHz, $CDCl_3$): δ_C 175.99 (2C), 169.70, 137.67, 127.18, 124.84, 123.33, 120.90, 29.16, 28.37(2C).ESIMS(-): *m/z* 261([M-H]$^-$); MS/MS (261): *m/z* 229, 188. EIMS *m/z*(%): 262(M$^{+\cdot}$, 100), 177(11); HRMS(EI): 262.04040±0.0020 ($C_{12}H_{10}N_2O_3S$, calcd 262.04121).

1-(2-Oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)-1*H*-pyrrole-2,5-dione (6c). Yellow solid, Yield: 78%, mp 127-128 °C. IR (neat) ν_{max} 1751w, 1724m, 1676m, 1627m, 1546m, 1487s, 1439m, 1397w, 1260w, 1187s, 977m, 927w, 893w, 848vs, 812m, 799s, 718s, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42(1H, d, *J* 2.0 Hz, H-7), 7.31(1H, dd, *J* 8.4, 2.0 Hz, H-5), 7.11(1H, d, *J* 8.4 Hz, H-4), 6.87(2H, s, CH=CH). ^{13}C NMR (100 MHz, $CDCl_3$+ 3% CD_3OD): δ_C169.37, 137.24, 134.32 8(C), 126.50, 124.60, 123.40, 120.59, 110.58. Significant long range correlations (HMBC): δ_H 6.94 with δ_C169.4 (CON).ESIMS(-): *m/z* 245([M-H]$^-$); MS/MS (245): *m/z* 217. EIMS *m/z*(%): 246 (M$^{+\cdot}$, 56), 171(7). HRMS(EI): 246.00871±0.0020 ($C_{11}H_6N_2O_3S$, calcd 246.00991).

1-(3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)-1*H*-pyrrole-2,5-dione(6d). Yellow solid, yield: 73%, mp 141-142 °C. IR (neat) ν_{max} 1716vs, 1683vs, 1586w, 1496s, 1402m, 1352w, 1325w, 1295w, 1255w, 1208w, 1149m, 1126m, 1051w, 1034w, 1006w, 873w, 828vs, 807w, 782w, 766w, 721m, 705w, 690vs, 649m cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.43(1H, d, *J* 2.0 Hz, H-7), 7.31(1H, dd, *J* 8.4, 2.0 Hz, H-5), 7.11(1H, d, *J* 8.4 Hz, H-4), 6.87(2H,s, CH=CH), 3.45(3H,s, *N*CH_3).^{13}C NMR (100 MHz, CD_3OD): δ_C 169.76, 169.37(2C), 137.24,134.32 (2C), 126.49, 124.53, 123.38, 120.57, 110.60,29.20. ESIMS(-): *m/z* 259([M-H]$^-$); MS/MS (259): *m/z* 231. EIMS *m/z*(%): 260(M$^{+\cdot}$, 50), 231(23); HRMS(EI): 260.02547±0.0020 ($C_{12}H_8N_2O_3S$, calcd 260.02556).

2-(2-Oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)isoindoline-1,3-dione (7a). White solid, yield: 68%, mp 155-156 °C. IR (neat) ν_{max}3138 w, 1822s, 1725vs, 1704vs, 1611w, 1502m, 1465w, 1398w, 1377m, 1321vs, 1272w, 1199w, 1155w, 1113m, 1087w, 1035s, 952w, 924w, 890w, 869w, 843s, 752m, 717vs, 707s, 656s, cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.18(1H, d, *J* 2.0 Hz, H-7), 7.96(2H, brs), 7.82(2H, brs), 7.39 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.21, 166.89 (2C), 142.15, 134.27(2C), 131.51 (2C), 128.95, 123.99 (2C), 127.05, 123.19, 116.14, 108.74. ESIMS(-): *m/z* 279([M-H]$^-$); MS/MS (279): *m/z* 159. EIMS *m/z*(%): 280(M$^{+\cdot}$, 100), 236(7); HRMS(EI): 280.04748±0.0020 ($C_{15}H_8N_2O_4$, calcd 280.04841).

2-(3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)isoindoline-1,3-dione (7b). White solid, yield: 66%, mp 198-199 °C. IR (neat) ν_{max} 1783s, 1715s, 1619w, 1509m, 1399w, 1372m, 1288w, 1265w, 1225w, 1170w, 1140w, 1102m, 1081m, 1047w, 948w, 935w, 887w, 866m, 813m, 793w, 747m, 719vs, 685m, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.96(2H, m), 7.80 (2H, m), 7.37(1H, d, *J* 2.0 Hz, H-7), 7.29(1H, dd, *J* 8.4, 2.0 Hz, H-5), 7.07(1H,d, *J* 8.4 Hz, H-4), 2.76 (3H, s, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.18, 166.85 (2C), 142.03, 134.27(2C), 131.49 (2C), 128.73, 123.97 (2C), 127.05, 123.08, 116.14, 108.78, 24.89. HMBC correlation: δ_H 2.76 (NCH_3): δ_C169.18. ESIMS(-): *m/z* 293([M-H]$^-$); MS/MS (293): *m/z* 278. EIMS *m/z*(%): 294(M$^{+\cdot}$,44), 279(3); HRMS(EI): 294.06286±0.0020 ($C_{16}H_{10}N_2O_4$, calcd 294.06406).

2-(2-Oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)isoindoline-1,3-dione (7c). White solid, yield: 79%, mp 153-154 °C. IR (neat) ν_{max}3147w, 1715vs, 1698vs, 1601w, 1484s, 1387m, 1367m, 1290s, 1222w, 1199m, 1154s, 1100m, 1082m, 1010m, 925w, 889w, 867m, 821m, 785w, 743w, 712vs, 667m, 605m, cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ_H8.46(1H, d, *J* 8.4 Hz, H-4), 7.96(2H, brs), 7.81(2H, brs), 7.52(1H, brs, H-7), 7.46(1H, brd, *J* 8.4 Hz, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C170.71, 166.94 (2C), 134.94 (2C), 133.95, 131.55 (2C), 129.12, 125.19, 123.94 (2C), 122.60, 119.88. ESIMS(-): *m/z* 295([M-H]$^-$). EIMS *m/z*(%): 296(M$^{+\cdot}$,100), 268(7); HRMS(EI): 296.02491±0.0030 ($C_{15}H_8N_2O_3S$, calcd 296.02556).

2-(3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)isoindoline-1,3-dione (7d). White solid, yield: 69%, mp 211-212 °C. IR (neat) ν_{max}1715s, 1692vs, 1604w, 1586w, 1495s, 1468w, 1387s, 1351m, 1324m, 1288w, 1251w, 1214s, 1132w, 1100m, 1081m, 1050w, 1004, 888w, 865m, 814s, 743w, 715vs, 698m, 669m, cm^{-1}.^{1}H NMR (400 MHz, CDCl$_3$): δ_H 7.96(2H, m), 7.80(2H, m), 7.53(1H, d, *J* 1.9 Hz, H-7), 7.42(1H, dd, *J* 8.4, 1.9 Hz, H-5), 7.15(1H, d, *J* 8.4 Hz, H-4), 3.48(3H,s, NCH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ_C169.84, 167.24(2C), 137.38, 134.60 (2C), 131.64, 127.00, 125.04, 123.91 (2C), 123.36, 121.11, 110.60, 29.20.ESIMS(-): *m/z* 309 ([M-H]$^-$); MS/MS (309): *m/z* 294, 281. EIMS *m/z*(%): 310(M$^{+\cdot}$, 100), 296(4), 281 (44); HRMS(EI): 310.04023±0.0030 (C$_{16}$H$_{10}$N$_2$O$_3$S, calcd 310.04121).

General procedure for the microwave-assisted synthesis of imide derivatives, exemplified by1-(2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)pyrrolidine-2,5-dione (5c). A mixture of succinic anhydride (12.0 mg, 0.120 mmol) and amine **1c** (19.9 mg, 0.120 mmol) in trifluoroacetic acid (1 mL) was MW irradiated at 73 ^{o}C for 15 min. After a workup as described for the reactions carried out under conventional heating, imide **5c** was obtained (26.5 mg, 89%). Similar treatment of succinic anhydride with **1d** gave imides **5d**, of maleic anhydride **1c-d** gave **6c-d** and of phthalic anhydride with the amines **1b-d** gave **7b-d** (86-91%).

General procedure for the microwave-assisted synthesis of formamide derivatives 8-11, exemplified by *N*-(3-methyl-2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)formamide (8). Amine **1a** (30.0 mg, 0.2 mmol) was dissolved in formic acid (0.3 mL) and the reaction mixture was MW irradiated at 60 °C for 10 min. The progress of the reaction was monitored by TLC. Once the reaction was completed, the mixture was quenched with ice and extracted with ethyl acetate (x3). The combined organic phases were washed with saturated NaHCO$_3$ solution, dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo* to yield the product (38.6 mg), detected as a single UV-spot in TLC (silica gel, ethyl acetate: hexane = 6:4).

***N*-(3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)formamide (8).** White solid, yield: 93%, mp 106-108 °C. IR (neat) ν_{max}3274w, 1697s, 1650vs, 1547vs, 1492vs, 1420m, 1333s, 1309s, 1269m, 1237w, 1156m, 1136m, 814m,cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): cis/trans= 2:1; for cisform, δ_H 8.37(1H, d, *J* 1.6 Hz, H formyl), 7.87(1H, d, *J* 2.0 Hz, H-7), 7.43(1H, dd, *J* 8.4, 2.0 Hz, H-5), 7.32(1H, s, br, NH formyl), 6.96(1H, d, *J* 8.4 Hz, H-4), 3.43(3H, s, *N*CH$_3$); for trans form, δ_H8.57(1H, d, *J* 11.6 Hz, H formyl), 7.70(1H, s, br, NH formyl), 7.19(1H, d, *J* 2.0 Hz, H-7), 7.07(1H, dd, *J* 8.4, 2.0 Hz, H-5), 7.01(1H, d, *J* 8.4 Hz, H-4), 3.45(3H, s, NCH$_3$). ^{1}H NMR (400 MHz, CD$_3$OD): cis/trans= 5:1, [with minor trans in brackets] δ_H8.25 [8.64] (1H, brs, CHO), 7.90[7.83](1H, d, *J* 2.0 Hz, H-7), 7.49[7.41](1H, dd, *J* 8.4, 2.0 Hz, H-5), 7.19 (1H, d, *J* 8.4 Hz, H-4), 3.44 (3H,s, NCH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$), [with minor trans in brackets]: δ_C 162.37, 159.02[159.07], 134.58, 132.88, 123.29, 118.46[118.59], 114.67[111.37], 110.41[111.12], 29.06[29.21]. Significant HMBC correlation: cisHCO /159.02.ESIMS(-): *m/z* 207 ([M-H]$^-$); MS/MS (207): *m/z* 192. EIMS *m/z* (%): 208(M$^{+\cdot}$, 100), 179 (20), 151 (62); HRMS(EI): 208.03027±0.0030 (C$_9$H$_8$N$_2$O$_2$S, calcd 208.03065).

***N*-(3-Methyl-2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)formamide (9).** Pale brown solid, yield: 95%, mp 135-137 °C. IR (neat) ν_{max}3083w, 1772vs, 1709vs, 1502s, 1454m, 1361w, 1321s, 1291m, 1172w, 1058w, 974w, 934w, 814vs, 742s, 701, 589s, 543m,cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): cis/trans= 2:1; for cis form, δ_H 8.37(1H, d, *J* 1.6 Hz, H formyl), 7.62(1H, d, *J* 2.0 Hz, H-7), 7.19(1H, dd, *J* 8.0, 1.6 Hz, H-5), 6.90(1H, d, *J* 8.4 Hz, H-4), 3.39(3H, s, NCH$_3$); for trans form, δ_H 8.55(1H, d, *J* 11.6 Hz, H formyl), 7.27(d, *J* 2.0 Hz, 1H, H-7), 6.71(d, *J* 8.4 Hz, 1H, H-4), 6.50(dd, *J* 6.4, 1.6 Hz, 1H, H-5), 3.41(3H, s, *N*CH$_3$).^{1}H NMR (400 MHz, CD$_3$OD): cis/trans= 5:1, [with minor trans in brackets] δ_H 8.25 [8.63] (1H, brs, CHO), 7.72 (1H, d, *J* 2.0 Hz, H-7), 7.32 (1H, dd, *J* 8.4, 2.0 Hz, H-5), 7.12 (1H, d, *J* 8.4 Hz, H-4), 3.39 (3H, s, NCH$_3$). ESIMS(-): *m/z* 191 ([M-H]$^-$); MS/MS (191): *m/z* 176. EIMS *m/z* (%): 192(M$^{+\cdot}$, 100), 163 (16), 149 (16); HRMS(EI): 192.05323±0.0030 (C$_9$H$_8$N$_2$O$_3$, calcd 192.05349).

***N*-(2-Oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)formamide (10).** White solid, purified by PLC of crude product, yield: 82%, mp 168-170 °C. IR (neat) ν_{max}3078w, 1747vs, 1650vs, 1407s, 1326s, 1226m, 962s, 942s, 750s, 706s,cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): cis/trans= 5:2, [with minor trans in brackets when detectable] δ_H 8.25 [8.62] (1H, brs, CHO), 7.68 (1H, d, *J* 2.0 Hz, H-7), 7.25[6.99] (1H, brd, *J* 8.4Hz, H-5), 7.04 (1H, d, *J* 8.4 Hz, H-4); ^{13}C NMR (100 MHz, CD_3OD), [with minor in brackets when detectable]: δ_C 165.04[161.49], 157.27 134.15, 128.18, 116.80[116.26] 110.69 [111.29], 103.93. Significant HMBC correlations:δ_H8.25/ δ_C134.15(C6); 7.25/110.69(C7), 7.04/116.80(C5). EIMS *m/z* (%): 178(M$^{+\cdot}$, 100), 150 (27); HRMS(EI): 178.03772±0.0030 ($C_8H_6N_2O_3$, calcd 178.03784).

***N*-(2-Oxo-2,3-dihydrobenzo[*d*]thiazol-6-yl)formamide(11)**. White solid, purified by PLC of crude product, yield: 86%. IR (in MeOH) ν_{max}1681s, 1491m, 1033m, 801w, cm^{-1}.^{1}H NMR (400 MHz, CD_3OD): cis/trans= 4:1, [with minor trans in brackets when detectable] δ_H 8.24[8.61](1H, brs, CHO), 7.83(1H, d, *J* 2.0 Hz, H-7), 7.39 (1H, brd, *J* 8.4Hz, H-5), 7.09(1H, d, *J* 8.4 Hz, H-4).^{13}C NMR (100 MHz, CD_3OD) [with minor in brackets when detectable]: δ_C171.87, 160.05, 133.14[133.17], 132.87, 124.37,118.52[117.88], 111.30.Significant correlations, HSQC: δ_H8.24/ δ_C160.05; HMBC: δ_H 8.24/ δ_C132.87(C6).^{1}H NMR (400 MHz, DMSO-d_6): cis/trans= 3:1, for cis form, δ_H 11.78 (very brs, NH), 10.18 (1H, brs), 8.23 (1H, brs, CHO), 7.86(1H, brs, H-7), 7.38(1H, brd, *J* 8.4Hz, H-5), 7.05(1H, d, *J* 8.4 Hz, H-4); for trans form, δ_H 11.78 (very brs), 10.09 (1H, d, *J* 11.5 Hz, NH formyl), 8.63 (1H, d, *J* 11.5 Hz, CHO), 7.38(1H, brd, *J* 8.4Hz, H-5), 7.05(1H,d, *J*8.4Hz, H-4).EIMS *m/z* (%): 194(M$^{+\cdot}$, 100), 166 (22); HRMS(EI):194.01341±0.0030 ($C_8H_6N_2O_2S$, calcd 194.01500).

Acknowledgments

This work was supported by Algerian Ministry of Higher Education and Scientific Research.
We are grateful to Adriano Sterni, University of Trento, for recording mass spectra.

Supplementary Material

Supplementary material is available.

References

1. Poupaert, J.; Carato, P.; Colacino.*Curr. Med. Chem*. **2005**, *12*, 877–885.
https://doi.org/10.2174/0929867053507388
2. Unlu, S.;Baytas, S. N.;Kupeli, E.;Yesilada, E.*Archiv. Pharm.* **2003**, *336*, 310-321.
https://doi.org/10.1002/ardp.200300748
3. Unlu, S.; Onkol, T.;Dundar, Y.; Okcelik, B.; Kupeli, E.;Yesilada, E.; Noyanalpan, N.; Sahin, M. F. *Arch. Pharm. Pharm. Med. Chem*. **2003**, *336*, 353-361.
https://doi.org/10.1002/ardp.200300746
4. Cicekli, S.U.; Onkol, T.; Ozgen, S.; Sahın, M.F. *Rev.Roum. Chim.* **2012**, *57*, 187-195.
5. Aichaoui, H.; Guenadil, F.; Kapanda, C. N.; Lambert, D. M.; McCurdy, C. R.; Poupaert, J. *Med. Chem. Res*. **2009**, *18*, 467-476.
https://doi.org/10.1007/s00044-008-9143-y
6. Petrov, O.; Ivanova, Y.; Momekov, G.; Kalcheva, V. *Lett. Drug Discov*. **2008**, *5*, 358-361.
https://doi.org/10.2174/157018008785777342

7. Ivanova, Y.; Momekov, G.; Petrov, O.; Karaivanova, M.; Kalcheva, V. *Eur. J. Med. Chem*. **2007**, *42*, 1382–1387.
https://doi.org/10.1016/j.ejmech.2007.02.019
8. Önkol, T.; Dündar, Y.; Yıldırım, E.; Erol, K.; Şahin, M. F. *Arzneimittelforschung* **2012,** *62*, 571–575.
https://doi.org/10.1055/s-0032-1327613
9. Ferreira, S. H.; Lorenzetti, B. B.; Devissaguet, M.; Lesiuer, D.; Tsouderos, Y. *Br. J. Pharmacol*. **1995**, *114*, 303–308.
https://doi.org/10.1111/j.1476-5381.1995.tb13227.x
10. Gülseven, Sıdır, Y.; Sıdır, İ.; Taşal, E.; Öğretir, C. *Int. J. Quantum Chem*. **2011**, *111*, 3616-3629.
11. Gülseven, Sıdır, Y.; Sıdır, İ. *J. Mol. Struct*. **2013**, *1045*, 131-138.
12. Unal, A. S.; Onurdag, F. K.; Ozgen, S.; Dogruer, D.; Onkol, T. *Indian J.Chem.B*, **2015**, *54B*, 253-259.
13. Carato, P.; Yous, S.; Sellier, D.; Poupaert, J.H.; Lebegue, N.; Berthelot, P. *Tetrahedron* **2004**, *60*, 10321-10324.
https://doi.org/10.1016/j.tet.2004.08.070
14. Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66–77.
15. Lukasik, N.; Wagner-Wysiecka, E.*Curr. Org. Synthesis* **2014**, *11*, 592-604.
https://doi.org/10.2174/15701794116661403211808578
16. Rajak, H.; Jain, D. K.; Dewangan, P. K.; Patel, V.; Agrawal N.*RGUHS J. Pharm. Sci.* **2013**, *3*, 14-20.
17. Das, R.; Mehta, D.; Bhardawaj, H. *Int. J. Res. Dev. Pharm. Life Sci*. **2012**, *1*, 32-39.
18. Defant, A.; Guella, G.; Mancini , I. *Synth. Commun*.**2008**, *38*, 3003–3016.
https://doi.org/10.1080/00397910802044249
19. Mader, D.; Liebeke, M.; Winstel, V.; Methling, K.; Leibig, M.; Götz, F.; Lalk, M.; Peschel, A. *BMC Microbiol.* **2013**, *13*, 7.
https://doi.org/10.1186/1471-2180-13-7
20. Jiang, T.; Zhou, X.; Taghizadeh, K.; Dong, M.; Dedon, P. C. *Proc. Natl. Acad. Sci. USA*, **2007**, *104*, 160-165.
21. Fischer, G. *Chem. Soc. Rev*.**2000**, *29*, 119–127.
https://doi.org/10.1039/a803742f
22. Lesieur, D.; Carato, P.; Bonte, J.-P.; Depreux, P.; Caignard, D.-H.; Millan, M.; Newman-Tancredi, A.; Renard, P.; Rettori, M.-C. *Eur. Pat. Appl*. 841330A119980513, 1998; Chem. Abstr. **1998**, *129*, 4662.
23. Domagalina, E.; Bien, I.; Zawisza, P. *Acta Pol. Pharm*. **1981**, *38*, 427-431.
24. Geronikaki, A.; Satiropoulou, E. *Res. Commun. Chem. Pathol. Pharmacol*. **1993**, 79, 355–362.
25. Bourn, A. J. R.; Gillies, D. G Randall, E. W. *Tetrahedron* **1964**, *20*, 1811-1818.
https://doi.org/10.1016/S0040-40200198450-9
26. Quintanilla-Licea, R.; Colunga-Valladares, J. F.; Caballero-Quintero, A.; Rodríguez-Padilla, C.; Tamez-Guerra, R.; Gómez-Flores, R.; Waksman, N. *Molecules* **2002**, *7*, 662-673.
https://doi.org/10.3390/70800662
27. Ilieva, S.; Hadjieva, B.; Galabov, B. *J.Mol. Struct*. **1999**, *476*, 151–156.
https://doi.org/10.1016/S0022-28609800542-0
28. Ottaviani, P.; Melandri, S.; Maris, A.; Favero, P. G.; Caminati, W. *J.Mol. Spectrosc*. **2001**, *205*, 173–176.
https://doi.org/10.1006/jmsp.2000.8243
29. Kubelka, J.; Keiderling, T.A. *J. Phys. Chem. A.* **2001**, *105*, 10922-10928.
https://doi.org/10.1021/jp013203y
30. Hayashi, T.; Zhuang, W.; Mukamel, S. *J. Phys. Chem. A.* **2005**, *109*, 9747-9759.

https://doi.org/10.1021/jp052324l

31. Frisch, M.J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, Jr T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; HratchianHratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian Revision E.01*, Gaussian, Inc., Wallingford, CT, **2004**.
32. Becke, A. D. *Phys. Rev. A.* **1988**, *38*, 3098-3100. https://doi.org/10.1103/PhysRevA.38.3098
33. Perdew, J. P.; Wang, Y. *Phys. Rev. B.* **1992**, *45*, 13244-13249. https://doi.org/10.1103/PhysRevB.45.13244
34. Ceperley, D. M.; Alder, B. *J. Phys. Rev. Lett.* **1980**, *45*, 566-569. https://doi.org/10.1103/PhysRevLett.45.566