Accepted Manuscript

"On water" ultrasound-assisted one pot efficient synthesis of functionalized 2-oxo-benzo [1, 4] oxazines: First application to the synthesis of anticancer indole alkaloid, Cephalandole A

Pradeep K. Jaiswal, Vashundhra Sharma, Jaroslav Prikhodko, Irina V. Mashevskaya, Sandeep Chaudhary

PII: S0040-4039(17)30352-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.03.048
Reference: TETL 48749

To appear in: *Tetrahedron Letters*

Received Date: 2 February 2017
Revised Date: 15 March 2017
Accepted Date: 16 March 2017

Please cite this article as: Jaiswal, P.K., Sharma, V., Prikhodko, J., Mashevskaya, I.V., Chaudhary, S., "On water" ultrasound-assisted one pot efficient synthesis of functionalized 2-oxo-benzo [1, 4] oxazines: First application to the synthesis of anticancer indole alkaloid, Cephalandole A, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.03.048

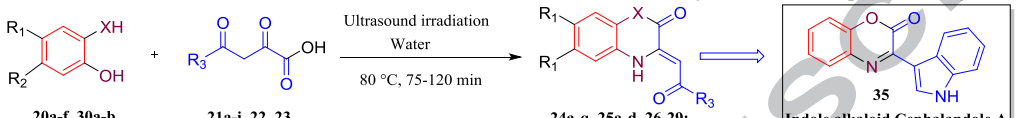
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

"On water" ultrasound-assisted, one-pot efficient synthesis of functionalized 2-oxo-benzo [1, 4] oxazines: First Application to the synthesis of anticancer indole alkaloid, Cephalandole A

Leave this area blank for abstract info.

Pradeep K. Jaiswal, [a,‡] Vashundhra Sharma,[a,‡] Jaroslav Prikhodko,[b] Irina V. Mashevskaya,[b] and Sandeep Chaudhary [a, c*]



One pot synthesis
green protocol
water as solvent
high yielding
column-chromatography free synthesis

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

"On water" ultrasound-assisted one pot efficient synthesis of functionalized 2-oxo-benzo [1, 4] oxazines: First application to the synthesis of anticancer indole alkaloid, Cephalandole A

Pradeep K. Jaiswal, [a,‡] Vashundhra Sharma,[a,‡] Jaroslav Prikhodko,[b] Irina V. Mashevskaya,[b] and Sandeep Chaudhary [a, c*]

[a]*Department of Chemistry, Malaviya National Institute of Technology, Jawaharlal Nehru Marg, Jaipur-302017, India.*
[b]*Department of Organic Chemistry, Faculty of Chemistry, Perm State University, 15 Bukireva, Perm 614990, Russian Federation*
[c]*Materials Research Centre, Malaviya National Institute of Technology, Jawaharlal Nehru Marg, Jaipur-302017, India.*
E-mail: schaudhary.chy@mnit.ac.in
‡Both authors have equal contribution.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Sonochemistry, green protocol
water as solvent, 2-oxo-benzo [1, 4] oxazines
2-oxo-quinoxaline, Cephalandole A

ABSTRACT

For the first time, an efficient, simple, synthetic green protocol for the one-pot synthesis of functionalized 2-oxo-benzo [1, 4] oxazines **24**-**29** in water under ultrasound irradiation is presented. As compared to conventional methods, the present protocol avoids traditional chromatography and purification steps and furnished the target molecules in excellent yields (upto 98%) with no side products. The methodology was also demonstrated on gram scale synthesis. Moreover, functionalized 2-oxo-quinoxaline analogues **31**-**33**, another class of bio-active heterocyclic scaffolds, were also prepared using this method. For the first time, this protocol was successfully applied in the synthesis of the anticancer indole alkaloid, Cephalandole A **35**.

Introduction

Water is a versatile solvent for many chemical reactions and becomes very valuable for organic chemists, because it is safe, cheap, environmentally benign, readily available, non-flammable, non-toxic and also in respect of isolation procedure of desired products (because most of the organic compounds are insoluble in water and they may be isolated in pure form only by filtration and/or recrystallization for avoiding column chromatography with hazardous solvents).[1] "On water" synthesis, firstly given by Barry K. Sharpless (2005),[2] is a unique concept of showing higher reactivity by the organic compounds in aqueous medium. Generally, reactions in water require vigorous stirring of water-insoluble reagents as they are not miscible in water due to the absence of organic co-solvents. This concept introduces the fact that reaction those occur in high yields in water, is due to the dual role played by water as a solvent and as a catalyst, in catalyzing the reaction.[1b-c, 3]

Ultrasound irradiation has been recognized as a clean and advantageous greener approach to accelerate organic reactions.[4] The salient features of the ultrasound-assisted reactions are higher reaction rates, formation of products in higher yield and selectivity, milder reaction conditions and shorter reaction time. Moreover, this technique is capable to activate many organic synthetic transformations due to acoustic cavitational collapse. In comparison to conventional heating, which provides thermal energy into the macro system; ultrasound irradiation reduces reaction time, increases yield, minimize waste and involve energy conservation by providing the activation energy to micro environment which emphasizes its greener significance.[5]

Benzo[1, 4]oxazines **1** and 2-oxo-benzo[1, 4]oxazines **2** are an important class of heterocycles which are found in many natural products as well as in several biologically active and medicinally important molecules.[6] Natural products such as blepharin **3**,[7] Cephalandole A **4**,[8a-d] C-1027-chr **5**,[9] and other pharmaceuticals incorporating 2H-1,4-benzoxazine-3(4H)one key scaffolds **6**-**9**, exhibit a wide range of biological activities such as potential activity against several diseases including heart disease,[10] an inhibitor of bacterial histidine protein kinase,[11] serotonin-3(5-HT_3) receptor antagonists,[12] neurodegenerative agents,[13] antihypertensive agents,[14] inflammatory agents,[15] analgesic,[16] D2 receptor antagonists,[17] antimycobacterial,[18] and antifungal agents.[19] (Figure 1)

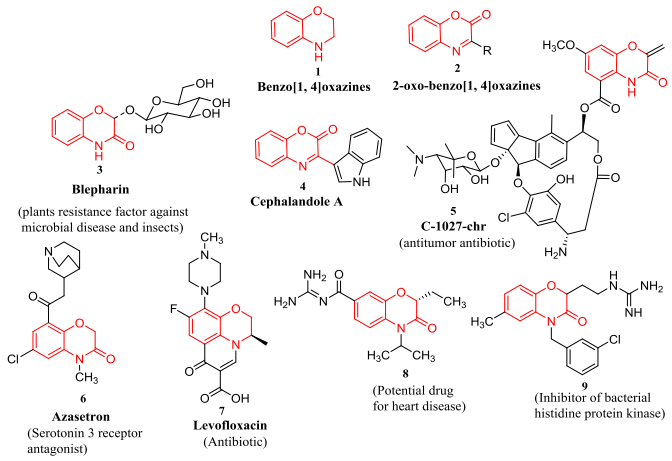
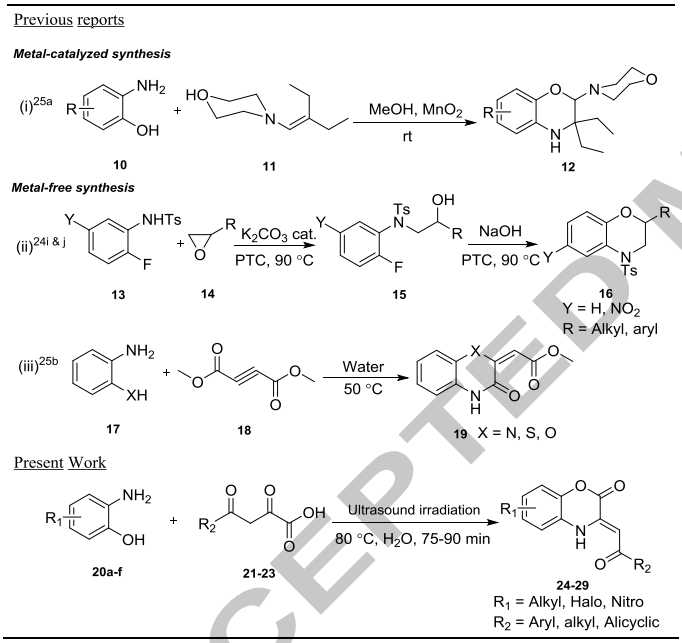


Figure 1. Structures of some natural products **3**-**5** and pharmaceutically active compounds **6**-**9** possessing 1, 4-benzoxazine scaffolds.

A number of synthetic approaches for the synthesis of benzo[1,4]oxazines, 2-oxo-benzo[1,4]oxazines and similar moieties have been reported over the past few decades.[20-24] In general, 2-oxo-benzo[1,4]oxazines and similar derivatives are

synthesized by the treatment of *o*-aminophenols with either *α*-ketoesters,[24a-c] or with domino reaction of substituted β-nitroacrylates[24h] or with alkyl propiolates.[24f] Another method involves synthesis of the 2-oxo-3-aryl-benzo[1,4]oxazines by condensation of arylacetates with methyl-o-quinonemonoximes.[24d-e] Furthermore, 4-alkyl- and 4-benzyl-3,4-dihydro-1,4-benzoxazin-2-one derivatives were also synthesized from reaction between an aldehydes and ethyl 2-(2-hydroxyphenylamino)acetate.[24g] In addition, a special type of MnO_2 catalysed tandem oxidation-inverse electron demand Diels Alder (IEDDA) reaction of o-aminophenol derivatives **10** with enamines **11** had also been reported to synthesize substituted 3,3-dialkyl-1,4-benzoxazines **12** with complete regiochemical control (Scheme 1, reaction–i).[25a] All these methodologies were associated with several drawbacks such as the use of toxic catalysts[23e] and starting materials, hazardous organic solvents, somewhat multistep and requirement of complicated reaction assembly, limited number of appropriate substrates for diverse synthesis,[25] tedious workup and low yields etc. Hence, green protocols having large substrate scope and wide diversification along with functional group compatibility as well as versatile nature for the synthesis of such bioactive moieties are in great demand.



Scheme 1. Previous and present approaches for the synthesis of substituted 1, 4-benzoxazines.

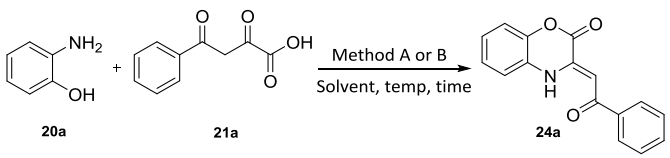
So far, there is no green protocol available in the literature using ultrasonic-assisted "on water" synthesis of these 2-oxo-benzo[1,4]oxazines. Earlier, Albanese *et. al.* reported a sequential two-step reaction involving $R_4N^+F^-$ directed ring opening of epoxides **14** with aryl sulfonamides **13** followed by *in situ* cyclization of **15** to synthesize 2-alkyl/aryl substituted 3,4-dihydro-2H-1,4-benzoxazines **16** in simple mild conditions (Scheme 1, reaction–ii).[24i&j] Further, recently, a green protocol for the synthesis of 3-oxo-1,4-benzoxazine derivatives **19** have also been developed via the reaction of o-substituted anilines **17** with dimethyl but-2-ynedioate **18**.[25b] However, this methodology is associated with limited diversification (Scheme-1, reaction–iii).

It is noteworthy that most of the earlier methods report the synthesis of 3-oxo-1,4-benzoxazines or 3-substituted 1,4-benzoxazines using greener approach whereas no green synthesis using water as a solvent under ultrasonic irradiation is reported for 2-oxo-1,4-benzoxazines. Herein, we report a simple, efficient, '*'on water*'' ultrasound-assisted, catalyst free, diverse one-pot synthesis of highly functionalized 2-oxo-benzo[1,4]oxazines **24-29** (Scheme 1, reaction–iv). This protocol involve one-pot reaction of substituted 2-aminophenol **20a-f** and substituted 2, 4-dioxo-4-phenylbutanoic acid **21-23** *on water* under ultrasound irradiation at 80 °C for 75-120 min, which furnished substituted 2-oxo-benzo[1,4]oxazines **24-29**, respectively upto 98% yields. Compounds **24a-g**, **24i-j**, **31a-b** had been prepared earlier by known procedures.[21] To the best of our knowledge, this is the first report of "*on water*" ultrasonic-assisted green synthesis of functionalized 2-oxo-benzo[1, 4]oxazines and its derivatives in excellent yields.

Results and discussion

Initially, we performed the model reactions between 2-aminophenol **20a** (0.1 mmol) and 2,4-dioxo-4-phenylbutanoic acid **21a** (0.1 mmol) in several polar solvents (2.0 mL) at room temperature for 120 min. The condensation product **24a** in isopropanol was isolated in only 16% yield; but when the same reaction was performed under ultrasound irradiation for 45 min at room temperature then, to our surprise, we obtained **24a** in 46 % yield (entry 1, Table 1). Further for getting the better yield, we subjected the same reaction at 90°C under conventional as well as in ultrasound irradiation for 120 min and 45 min respectively, which afforded **24a** in 39 % and 62 % yield, respectively (entry 1, Table 1). After obtaining the improved yield under ultrasound irradiation, we anticipated that ultrasound irradiation could potentially accelerate the reaction and increase yields. Thus, these results prompted us to investigate in detail the effect of sonication, temp, time and solvent on the rate and yield of the reaction. The obtained condensed product **24a** was fully characterized by their spectroscopic data (^{1}H and ^{13}C NMR, HRMS and IR).

Table 1. Optimization study [a]: Synthesis of 2-oxo-benzo[1,4]oxazines **24a** by the reaction of 2-aminophenol **20a** and 2, 4-dioxo-4-phenylbutanoic acid **21a**



Entry	Solvent	Temp (°C)	Method A[b]		Method B[c]	
			Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)
1	Isopropanol	rt	120	16	45	46
2	Isopropanol	90	120	39	45	62
3	EtOH	rt	120	22	45	44
4	EtOH	80	120	52	45	70
5	DMF	80	120	61	45	78
6	DMSO	80	120	64	45	73
7	Diethylene glycol	80	120	60	45	81
8	H_2O	rt	120	12	45	62
9	H_2O	80	120	69	45	86
10	H_2O	100	120	73	45	89
11	H_2O	80	240	78	60	94
12	H_2O	80	300	82	**75**	**98**
13	H_2O	80	360	80	90	97

[a] *Reaction condition*: **20a** (0.1 mmol), **21a** (0.1 mmol) in solvent (2.0 mL), at given time and temp under method A or B; [b] **Method A**: Conventional heating; [c] **Method B**: Ultrasound Irradiation; [d]Isolated yield after recrystalization/column chromatography.

In order to increase the yield of the desired 2-oxo-benzo[1,4]oxazine **24a**, we did this reaction in EtOH, DMF, DMSO, Diethylene glycol, water etc. at different temperature using method A as well as method B. As can be seen from the

table 1; yield was significantly improved under ultrasonic conditions (method B) as compared to conventional method (method A) conditions (entries 3-8; Table 1). So, we performed our model reaction in water as solvent only (entries 8-13). When we performed our model reaction on water at room temp for 120 min and under ultrasound irradiation for 45 min, we obtained **24a** in 12 % and 62 % yield, respectively (entry 8, Table 1). Then, we carried out the model reaction under heating at 80 °C under conventional as well as under ultrasound irradiation conditions; **24a** was obtained in 69 % and 86 % yield respectively (entry 9, Table 1). Either on further increasing the reaction temperature from 80°C to 100 °C or increasing /decreasing the reaction time, under conventional heating, there was slight improvement in yields ranging from 73-80 % (entries 10-13, Table 1). But, to our delight, the yield of desired product **24a** was increased up to 98 % when time was extended from 45 to 75 min. under ultrasonic irradiation conditions (entries 10-12, Table 1). On further extending the time from 75 min to 90 min at the same reaction conditions, i.e. at 80 °C temp under ultrasound irradiation condition, yield of **24a** dropdown slightly to 97 % (entries 13, Table 1). Thus, based on above screening studies, water as solvent, 80°C temperature for 75 min was found to be the best optimized reaction condition under ultrasound irradiation for the synthesis of desired 2-oxo-benzo[1,4]oxazines **24a** (entry 12, Table 1).

The proposed mechanism of this optimized reaction might involves intermolecular condensation followed by an intramolecular condensation *via* either **path A** or **path B**. This can be explained by taking **24a** as reference example, which is formed by the reaction between **20a** and **21a,** (Figure 2). The H-bonding between the oxygen atom of water and the phenolic hydrogen of 2-aminophenol increased the nucleophilicity of the oxygen atom of the 2-aminophenol (**20aa'**). On the other hand, the hydrogen bond between hydrogen atom of water and carboxylic oxygen increased the electrophilic character of carbon adjacent to the carbonyl group (**21aa'**).Therefore, according to **path A**; in the probable intermediate (**I**), the nucleophilic attack at the carboxylic carbon atom by the phenolic oxygen (**II**) followed by removal of water led to conjugated acyclic adduct (**III**). Then, the second nucleophilic attack of nitrogen atom to the carbonyl carbon adjacent to newly formed ester linkage of this acyclic adduct took place (**IV**) and the corresponding 2-oxo-benzo[1,4]oxazine **24a** was obtained followed by the removal of second water molecule. Whereas, contrary to this, as depicted in **path B**; firstly the nucleophilic attack by nitrogen of aminophenol **20aa'** at the carbonyl carbon (adjacent to the carboxylic group) of **21aa'** led to the intermediate **(V)**, which on removal of the water molecule gets converted to the conjugated acyclic adduct (**VIII**). Finally, the desired product 2-oxo-benzo[1,4]oxazine **24a** was obtained after the second nucleophilic attack by phenolic oxygen at carboxylic carbon followed by removal of second water molecule from intermediate **(IX)**.

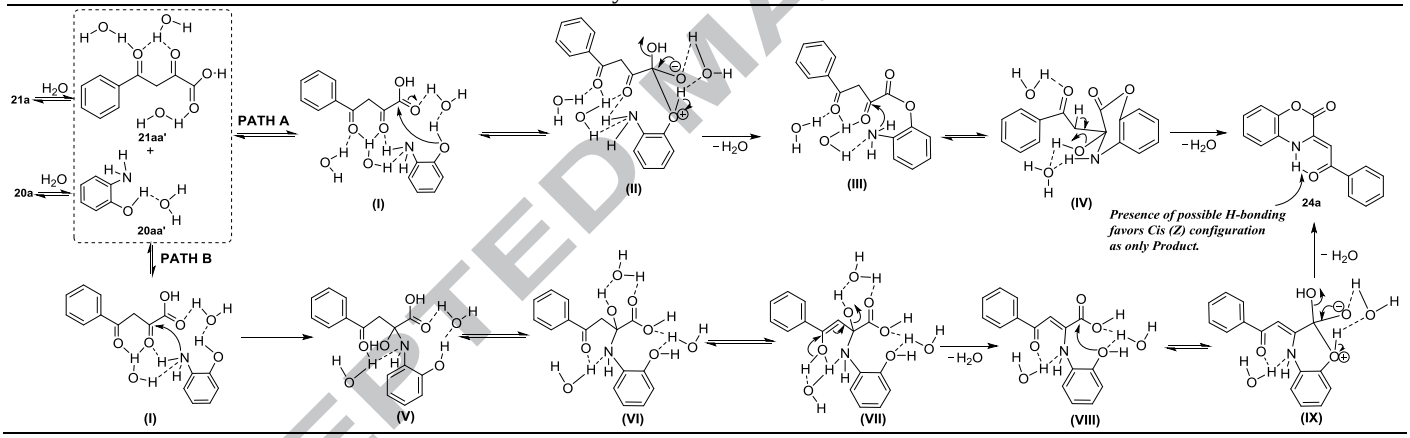


Figure 2. Probable mechanism for the synthesis of 2-oxo-benzo[1,4]oxazine **24a**.

Substrate scope and versatility

The generality and versatile nature of our optimized reaction conditions was then investigated. Several alkyl/halide/nitro-substituted 2-aminophenol **20a-f** was reacted with alkoxy/ alkyl/halide/nitro-substituted 2, 4-dioxo-4-phenylbutanoic acid **21a-i** and **22-23** in water in excellent yields (upto 98%) under our optimized conditions furnished the desired 2-oxo-benzo[1,4]oxazines **24a-q, 25a-d** and **26-29**, respectively (Scheme 2, figure 3).[26] All the compounds were purified either by flash column chromatography method or by recrystallization method (see experimental section).

The electron donating substituents present (**20b** or **20e**) on 2-aminophenol increases the yields, while the electron withdrawing substituents (as in **20c, 20d** and **20f**) slightly decreases the yields of products. The same trend of isolated yield was also obtained with electron donating (**21a-h**) and electron withdrawing substituents (**21i**), which was present on 2,4 -dioxo-4-phenylbutanoic acid **21a-i**. In the case of polycyclic (aromatic as well as aliphatic) diketo acids i.e., **22** and **23a** and aliphatic diketo acid **23b**; **25a-d, 26** and **27** were obtained in excellent yields (86-93%) whereas **28** and **29** was obtained in 79% and 76% yields, respectively. Thus, these result shows that the aromatic diketo acids, **21a-i** and **22**, afforded the target 2-oxo-benzo[1,4]oxazines in high yields (upto 98%) as compared with that obtained from alicyclic diketo acids **23a** and alkyl diketo acids **23b**.

It has been also observed that the several functional groups, like F, Cl, Br, OMe and NO_2 are well tolerable under our reaction conditions as the desired products were obtained in high isolated yields indicating the versatility of the methodology.

Scheme 2. Ultrasound-assisted one-pot green synthesis of 2-oxo-benzo[1,4]oxazines **24a-q**, **25a-d** and **26-29**.[a]

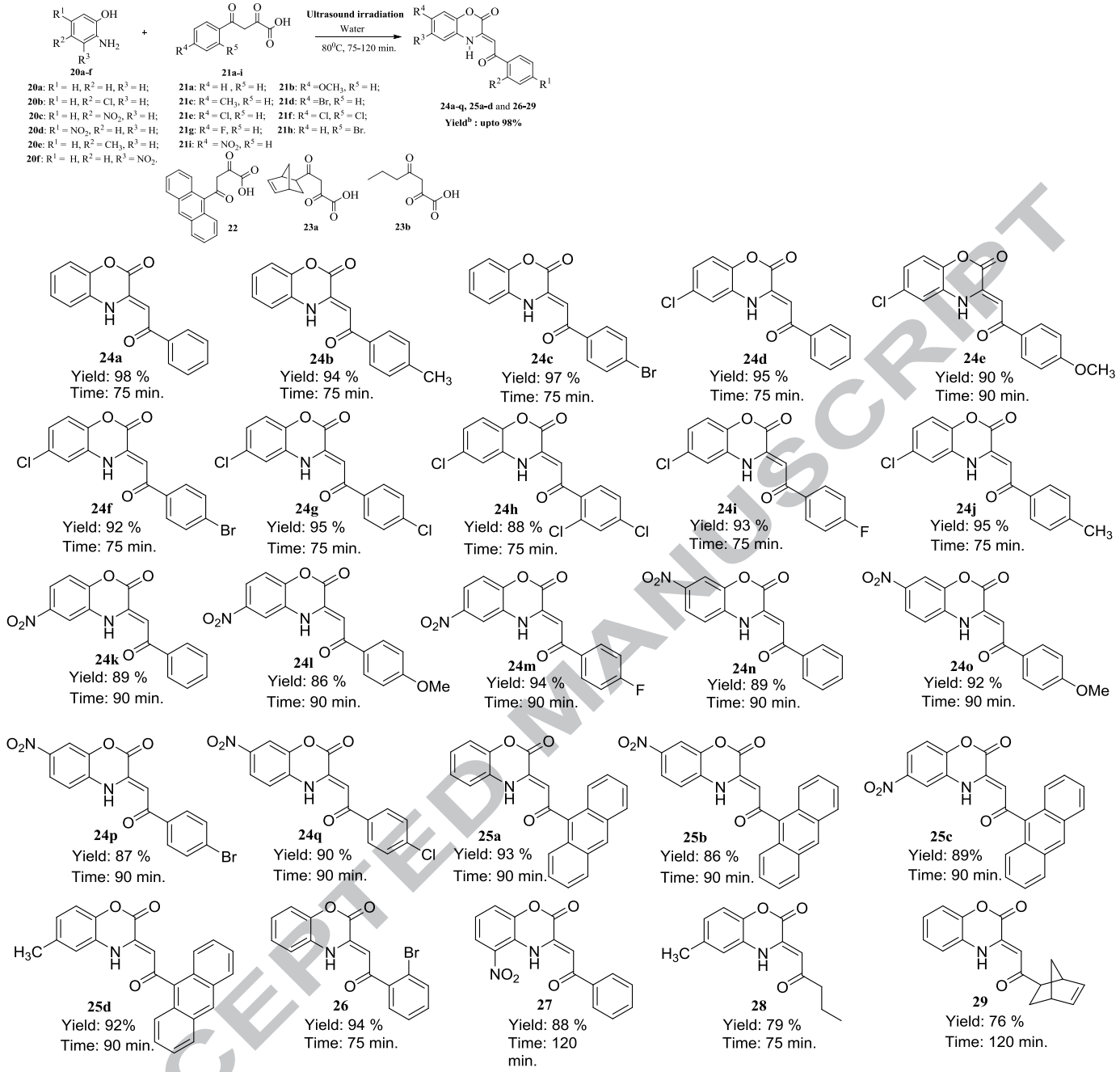
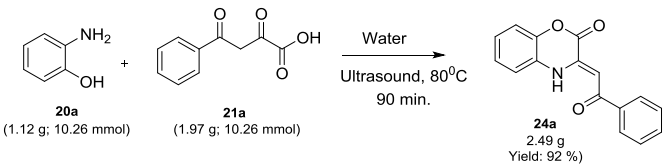


Figure 3. Structures of all synthesized 2-oxo-benzo[1,4]oxazines.

[a]Unless otherwise mentioned, all the reactions were carried out with substrates aminophenols **20a-f** (0.2 mmol) and **21- 23** (0.2 mmol) in water (2.0 mL) at 80 °C temperature at given time under ultrasound irradiation. [b]Isolated yield.

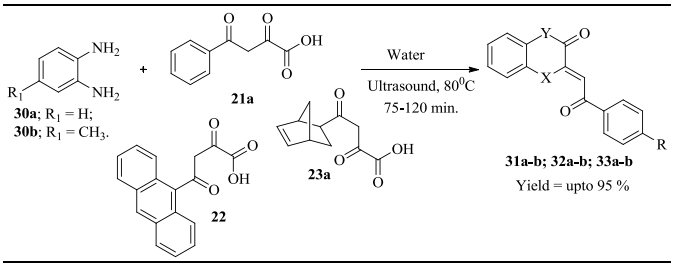
Furthermore, we demonstrated its practicality by performing the model reaction in gram scale. The gram scale synthesis was performed taking **24a** as representative example (Scheme 3). The heterogeneous reaction mixture of 2-amino phenol (**20a**, 1.12 g, 10.26 mmol) and 2,4-dioxo-4-phenylbutanoic acid (**21a**, 1.97 g, 10.26 mmol) in water was stirred and heated at 80 °C for 90 min under ultrasonic irradiations (monitored by TLC). The solid 2-oxo-benzo[1,4]oxazines **24a** was precipitated out, which was easily isolated in 92 % yield by simple filtration followed by washing and recrystallization with EtOH.

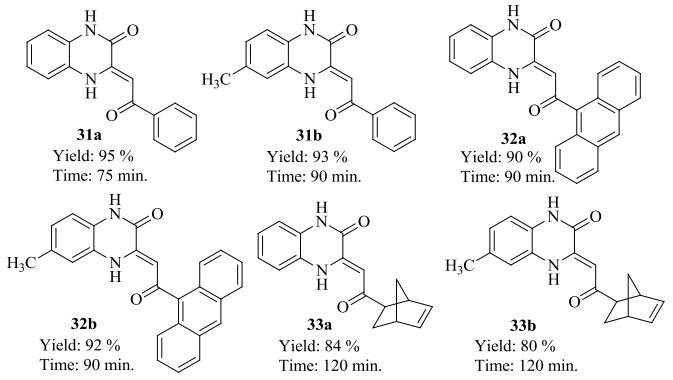


Scheme 3. Ultrasound-assisted gram scale synthesis of 2-oxo-benzo[1,4]oxazines **24a.**

After successful application of developed methodology for 2-oxo-benzo[1,4]oxazines class of molecules, the study was further extended to 2-oxo-quinoxaline class of molecules, an important class of heterocyclic bioactive compound present in various natural products. **30a-b** on reaction with several 2,4-dioxo-4-aryl/alicyclic acid **21a, 22** and **23a** furnished the corresponding substituted 2-oxo-quinoxaline analogues (**31a-b, 32a-b & 33a-b**) in excellent 80-95% yields under our optimized reaction conditions (Scheme 4).[27]

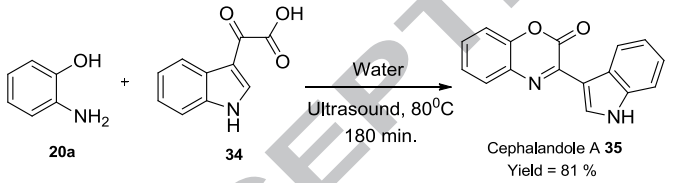
Scheme 4. Ultrasound-assisted one-pot green synthesis of 2-oxo- to 2-oxo-quinoxaline **31**-**33**.[a]





[a]Unless otherwise mentioned, all the reactions were carried out with substrates **30a-b** (0.2 mmol) and **21a, 22** and **23a** (0.2 mmol) in water (2.0 mL) at 80 °C temperature at given time under ultrasound irradiation. [b]Isolated yield.

Finally, we extended the application of our developed methodology in the synthesis of 2H-benzo[b][1,4]oxazin-2-one-based anticancer indole alkaloid, Cephalandole A. It was isolated from the Taiwanese orchid *Cephalanceropsis gracilis* (Orchidaceae) in 2006.[8a-d] The crude extract of this plant exhibited activity against lung (NCI-H460; IC_{50} = 7.8 µM), breast (MCF-7; IC_{50} = 7.57 µM) and CNS (SF-268; IC_{50} = 12.2 µM) carcinoma cell lines. Aminophenol **20a** on reaction with 3-indoleglyoxylic acid **34** in water under our optimized conditions furnished Cephalandole A **35** in 81 % yield.[28] (Scheme-5). The spectral data of **35** was found identical with the literature data.



Scheme 5. Synthesis of Cephalandole A **35.**

Conclusions

In summary, we have developed a simple, highly efficient green protocol for the synthesis of functionalized 2-oxo-benzo[1,4]oxazines **24a-q, 25a-d,** and **26-29** in excellent yields upto 98% under ultrasound irradiation conditions at 80 °C in 75-120 min. Moreover, this methodology tolerates a broad range of functional groups and their positions under simple reaction conditions, and provides a straightforward access to a library of functionalized 2-oxo-benzo[1, 4]oxazines analogues from readily available starting substrates. To the best of our knowledge, this is the first report of ultrasound assisted synthesis of functionalized 2-oxo-benzo[1,4]oxazines in water. In addition, functionalized 2-oxo-quinoxaline analogues **31a-b**, **32a-b** and **33a-b** were also synthesized utilizing this methodology in excellent yields (upto 95%). Gram scale synthesis and synthesis of Cephalandole A **35**, highlights the practicality of this methodology.

Acknowledgements

S. C. acknowledges MNIT Jaipur for providing necessary facilities. S.C also acknowledges CSIR, New Delhi for CSIR Grant [02 (0189)/14/EMR-II], DST, New Delhi for DST-RFBR Indo-Russian Joint Research Project (INT/RUS/RFBR/P-169) and SERB, New Delhi for SERB Fast track young scientist award (CS-037/2013). P. K. J. And V. S. thanks CSIR, New Delhi and MNIT, Jaipur respectively for providing financial assistance in the form of Research Associateship and institute fellowship, respectively. Materials Research Centre, MNIT, Jaipur is gratefully acknowledged for providing analytical facilities.

References and notes

1. (a) Chanda, A.; Fokin, V. V. *Chem. Rev*. **2009**, *109*, 725; (b) Butler, R. N.; Coyne, A. G. *Chem. Rev*. **2010**, *110*, 6302; (c) Simon, M. O.; Li, C. -J. *Chem. Soc. Rev*. **2012**, *41*, 1415.
2. Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **2005**, *44*, 3275.
3. (a) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc*. **2007**, *129*, 5492; (b) Beattie, J. K.; McErlean, C. S. P.; Phippen, C. B. W. *Chem. Eur. J*. **2010**, *16*, 8972; (c) Mellouli, S.; Bousekkine, L.; Theberge, A. B.; Huck, W. T. S. *Angew. Chem. Int. Ed*. **2012**, *51*, 7981.
4. (a) Cravotto, G.; Cintas, P. *Chem. Soc. Rev*. **2006**, *35*, 180–196; (b) Mason, T. J.; Lorimer, J. P. *Applied Sonochemistry: The Uses of Power Ultrasound in Chemistry and Processing, Wiley-VCH*, **2002,** 303; (c) Li, J. T.; Yin, Y.; Li, L.; Sun, M. X. *Ultra. Sonochem.* **2010**, *17*, 11–13.
5. (a) Ni, C. -L.; Song, X. -H.; Yan, H.; Song, X. -Q.; Zhong, R.-G. *Ultra. Sonochem*. **2010**, *17*, 367–369; (b) Bazgir, A.; Ahadi, S.; Ghahremanzadeh, R.; Khavasi, H. R.; Mirzaei, P. *Ultra. Sonochem*. **2010**, *17*, 447–452; (c) Vengatesan, M. R.; Devaraju, S.; Kannaiyan, D.; Kun Song, J.; Alagar, M. *Poly. Inter*. **2013**, *62* 127–133; (d) Azarifar, D.; Sheikh, D. *Chem. Hetero. Comp*. **2011**, *47*, 1128-1136.
6. (a) Teller J. and Schaumann, E. *Georg Thieme, Stuttgart, Houben-Weyl Methods of Organic Chemistry, Hetarenes IV, Six-Membered and Larger Hetero-Rings with Maximum Unsaturation, Ed*. **1997**, *E9a*, pp. 141–177; (b) Ila`s, J.; Anderluh, P. S.; Dolenc, M. S.; Kikelj, D. *Tetrahedron*, **2005**, *61*, 7325
7. (a) Hasui, T.; Matsunaga, N.; Ora, T.; Ohyabu, N.; Nishigaki, N.; Imura, Y.; Igata, Y.; Matsui, H.; Motoyaji, T.; Tanaka, T.; Habuka, N.; Sogabe, S.; Ono, M.; Siedem, C. S.; Tang, T. P.; Gauthier, C.; DeMeese, L. A.; Boyd S. A.; Fukumoto, S. *J. Med. Chem*. **2011**, *54*, 8616; (b) Matsuoka, H.; Ohi, N.; Mihara, M.; Suzuki, H.; Miyamoto, K.; Maruyama, N.; Tsuji, K.; Kato, N.; Akimoto, T.; Takeda, Y.; Yano K.; Kuroki, T. *J. Med. Chem*. **1997**, *40*, 105; (c) Bromidge, S. M.; Bertani, B.; Borriello, M.; Faedo, S.; Gordon, L. J.; Granci, E.; Hill, M.; Marshall, H. R.; Stasi, L. P.; Zucchelli, V.; Merlo, G.; Vesentini, A.; Watson J. M.; Zonzini, L. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 5653; (d) Bromidge, S. M.; Bertani, B.; Borriello, M.; Bozzoli, A.; Faedo, S.; Gianotti, M.; Gordon, L. J.; Hill, M.; Zucchelli, V.; Watson J. M.; Zonzini, L. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 2338; (e) Hasui, T.; Ohra, T.; Ohyabu, N.; Asano, K.; Matsui, H.; Mizukami, A.; Habuka, N.; Sogabe, S.; Endo, S.; Siedem, C. S.; Tang, T. P.; Gauthier, C.; De Meese, L. A.; Boyd S. A.; Fukumoto, S. *Bioorg. Med. Chem*. **2013**, *21*, 5983; (f) Chen, Q.; Chen, M.; Yu, C.; Shi, L.; Wang, D.; Yang Y.; Zhou, Y. *J. Am. Chem. Soc*. **2011**, *133*, 16432; (g) Rueping, M.; Antonchick A. P.; Theissmann, T. *Angew. Chem., Int. Ed*. **2006**, *45*, 6751; (h) Saitz, C.; Rodr´ıguez, H.; M´arquez, A.; Ca˜nete, A.; Jullian C.; Zanocco, A. *Synth. Commun*. **2001**, *31*, 135; (i) Miyabe, H.; Yamaoka Y.; Takemoto, Y. *J. Org. Chem*. **2006**, *71*, 2099.
8. (a) Wu, P.-L.; Hsu, Y.-L.; Jao, C.-W. *J. Nat. Prod*. **2006**, *69*, 1467; (b) Mason, J.; Bergman, J.; Janosik, T. *J. Nat. Prod*., **2008**, *71*, 1447; (c) Gross, L.; Mohn, F.; Moll, N.; Meyer, G.; Ebel, R.; Abdel-Mageed, W. M.; Jaspars, M. *Nat. Chem*. **2010**, *2*, 821; (d) Gross, L. *Nat. Chem*. **2011**, *3*, 273.
9. (a) Minami, Y.; Yosa, K.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett*. **1993**, *34*, 2633; (b) Dai, W. M. *Curr. Med. Chem*. **2003**, *10*, 2265-2283.
10. Tsutsui, H.; Hori, M.; Watanabe, I.; Harada, K.; Maruo, J.; Morita, T.; Ohtaka, H.; Yamamoto, T. *EP Patent Appl*. 719766, **1996**.
11. Frechette, R.; Weidner-Wells, M. A. *WO Patent Appl*. 9717333, **1997**.
12. Bromidge, S. M.; Arban, R.; Bertani, B.; Bison, S.; Borriello, M.; Cavanni, P.; Forno, G. D.; Di-Fabio, R.; Donati, D.; Fontana, S.; Gianotti, M.; Gordon, L. J.; Granci, E.; Leslie, C. P.; Moccia, L.; Pasquarello, A.; Sartori, I.; Sava, A.; Watson, J. M.; Worby, A.; Zonzini, L.; Zucchelli, V. *J. Med. Chem*. **2010**, *53*, 5827-5843.

13. (a) Lestage, P.; Lockhart, B.; Fleury, M. B.; Largeron, M.; *WO Patent Appl*. 9962889, **1999**; (b) Blattes, E.; Lockhart, B.; Lestage, P.; Schwendimann, L.; Gressens, P.; Fleury, M. B.; Largeron, M. *J. Med. Chem*. **2005**, *48*, 1282-1286.
14. Touzeau, F.; Arrault, A.; Guillaumet, G.; Scalbert, E.; Feiffer, B. P.; Rettori, M. C.; Renard, P.; Mérour, J. Y. *J. Med. Chem*. **2003**, *46*, 1962-1979.
15. (a) Khalaj, A.; Abdollahi, M.; Kebriaeezadeh, A.; Adibpour, N.; Pandi, Z.; Rasoulamini, S. *Ind. J. Pharmacol*. **2002**, *34*, 184-188; (b) Mashevakaya, I. V.; Anikina, L. V.; Vikharev, Y. B.; Safin, V. A.; Koltsova, S. V.; Maslivets, A. N. *Pharm. Chem. J*. **2001**, *35* 414-417.
16. (a) Kamble, R. D.; Hese, S. V.; Meshram, R. J.; Kote, J. R.; Gacche, R. N.; Dawane, B. S. *Med. Chem. Res*. **2015**, *24*, 1077-1088; (b) Gokhan, N.; Erdogan, H.; Durlu, N. T.; Demirdamar, R. *Farmaco*. **1999**, *54*, 112-115.
17. Wise, L. D.; Wustrow, D. J.; Belliotti, T.; *WO Patent Appl*. 9745419, **1997**.
18. (a) Waisser, K.; Perina, M.; Kunes, J.; Klimesova, V.; Kaustova, J. *Farmaco*. **2003**, *58*, 1137-1149; (b) Konda, S.; Raparthi, S.; Bhaskar, K.; Munaganti, R. K.; Guguloth, V.; Nagarapu, L.; Akkewar, D. M. *Bioorg. Med. Chem. Lett*. **2015**, *25*, 1643-1646.
19. Waisser, K.; Kubicova, L.; Buchta, V.; Kubanova, P.; Bajerova, K.; Jiraskova, L.; Bednařík, O.; Bureš, O.; Holý, P. *Folia Microbiol*. **2002**, *47*, 488-492.
20. (a) Stepanova, E. E.; Babenysheva, A. V.; Maslivets, A. N. *Russ. J. Org. Chem*. **2011**, *47*, 937-940; (b) Stepanova, E. E.; Aliev, Z. G.; Maslivets, A. N. *Russ. J. Org. Chem*. **2013**, *49*, 1762-1767; (c) Aliev, Z. G.; Krasnykh, O. P.; Maslivets, A. N.; Atovmyan, L. O. *Russ. Chem. Bull*. **2000**, *49*, 2045-2047;(d) Koini, E. N.; Papazafiri, P.; Vassilopoulos, A.; Koufaki, M.; Horváth, Z.; Koncz, I.; Virág, L.; Papp, G. J.; Varró, A.; Calogeropoulou, T. *J. Med. Chem*. **2009**, *52*, 2328-2340; (e) Ramesh, C.; Raju, B. R.; Kavala, V.; Kuo, C.-W.; Ya, C.-Fa. *Tetrahedron*, **2011**, *67*, 1187-1192; (f) Jangili, P.; Kashanna, J.; Das, B. *Tetrahedron Letters*, **2013**, *54*, 3453–3456; (g) Huo, C.; Dong, J.; Su, Y.; Tang, J.; Chen, F. *Chem. Commun*. **2016**, *52*, 13341—13344;(h) Feng, E.; Huang, H.; Zhou, Y.; Ye, D.; Jiang, H.; Liu, H. *J. Org. Chem*. **2009**, *74*, 2846; (i) Feng, G.; Wu, J.; Dai, W.-M. *Tetrahedron Lett*. **2007**, *48*, 401; (j) Yuan, Y.; Liu, G.; Li, L.;Wang, Z.;Wang, L. *J. Comb. Chem*. **2007**, *9*, 158; (k) Xing, X.; Wu, J.; Feng, G.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 6774; (l) Kundu, N. G.; Chaudhuri, G.; Upadhyay, A. *J. Org. Chem*. **2001**, *66*, 20; (m) Henry, N.; Guillaumet, G.; Pujol, M. D. *Tetrahedron Lett*. **2004**, *45*, 1465.
21. For known compounds, see: (a) Xia, M. Faming Zhuanli Shenqing Gongkai Shuomingshu, **2008**, CN 101108860 A; (b) Mashevskaya, I. V.; Tolmacheva, I. A.; Voronova, E. V.; Odegova, T. F.; Aleksandrova, G. A.; Goleneva, A. F.; Kol'tsova, S. V.; Maslivets, A. N. *Pharm. Chem. J*. (*Translation of Khimiko-Farmatsevticheskii Zhurnal*), **2002**, *36* (2), 33-35; (c) Iwanami, Y.; Seki, T.; Inagaki, T. *Bull. Chem. Soc. Jpn*. **1971,** *44* (5), 1316-1321; (d) Kozminykh, E. N.; Igidov, N. M.; Shavkunova, G. A.; Kozminykh, V. O. *Russ. Chem. Bull*. (*Translation of Izvestiya Akademii Nauk, Seriya Khimicheskaya*), **1997**, *46* (7), 1285-1290; (e) Gein, V. L.; Rassudikhina, N. A.; Shepelina, N. V.; Vakhrin, M. I.; Babushkina, E. B.; Voronina, E. V. *Pharm. Chem. J*. **2008**, *42* (9), 529-532; (f) Xia, M.; Wu, B.; Xiang, G. *J. Fluor. Chem*. **2008**, *129* (5), 402-408; (g) Habash, M.; Taha, M. O. *Bioorg. Med. Chem*. **2011**, *19* (16), 4746-4771; (h) Reynisson, J.; Court, W.; Neill, C. O.; Day, J.; Patterson, L.; McDonald, E.; Workman, P.; Katan, M.; Eccles, S. A. *Bioorg. Med. Chem*. **2009**, *17* (8), 3169-3176; (i) Maslivets, V. A.; Maslivets, A. N. *Russ. J. Org. Chem*. **2012**, *48* (9), 1233-1237 and references cited therein; (j) Lia, X.; Liua, N.; Zhanga, H.; Knudsonb, S. E.; Slaydenb, R. A.; Tongea, P. J. *Bioorg. Med. Chem. Lett*. **2010**, *20* (21), 6306-6309; (k) Khalturina, V. V.; Shklyaev, Yu. V.; Aliev, Z. G.; Maslivets, A. N. Russ. *J. Org. Chem*. **2009**, *45*g(10), 1519-1522.
22. For selected examples see: (a) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y. L. *Angew. Chem., Int. Ed*. **2001**, *40*, 207; (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Sugita, *J. Am. Chem. Soc*. **2002**, *124*, 2212; (c) Largeron, M.; Neudörffer, A.; Vuilhorgne, M.; Blattes, E.; Fleury, M.-B. *Angew. Chem. Int. Ed*. **2002**, *41*, 824; (d) Choudhary, G.; Naganaboina, R. T.; Peddinti, R. K. *RSC Adv*. **2014**, *4*, 17969; (e) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett* **2004**, 2449 and references therein; (f) Macias, F. A.; Marin, D.; Oliveros Bastidas, A.; Molinillo, J. M. G. *Nat. Prod. Rep*. **2009**, 26, 478; (g) Ilas, J.; Stefanic Anderluh, P.; Sollner Dolenc, M.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325 and references therein.
23. For selected recent examples, see: (a) Gabriele, B.; Salerno, G.; Veltri, L.; Mancuso, R.; Li, Z.; Crispini, A.; Bellusci, A. *J. Org. Chem*. **2006**, *71*, 7895; (b) Bhadra, S.; Adak, L.; Samanta, S.; Maidul Islam, A. K. M.; Mukherjee, M.; Ranu, B. C. *J. Org. Chem*. **2010**, *75*, 8533; (c) Brahma, K.; Sasmal, A. K.; Chowdhury, C. *Org. Biomol. Chem*. **2011**, *9*, 8422; (d) Ylijoki, K. E. O.; Kündig, E. P. *Chem. Commun*. **2011**, *47*, 10608; (e) Xia, M.; Wu, B.; Xiang G.-F. *Synthetic Communications*, **2008**, *38*, 1268–1278.
24. (a) Trebaul, C.; Roncali, J.; Garnier F.; Guglielmetti, R. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2657; (b) Moffet, R. B. *J. Med. Chem.* **1966**, *9*, 475; (c) Chilin, A.; Confente, A.; Pastorini G.; Guiotto, A. *Eur. J. Org. Chem.* **2002**, 1937; (d) Nicolaides, D. N.; Gautam, D. R.; Litinas, K. E.; Hadjipavlou-Litina D. J.; Kontogiorgis, C. A. *J. Heterocycl. Chem.* **2004**, *41*, 605; (e) Nicolaides, D. N.; Awad R. W.; Varella, E. A.; *J. Heterocycl. Chem.* **1996**, *33*, 633; (f) Yavari, I.; Souri, S.; Sirouspour M.; Djahaniani, H. *Synthesis*, **2006**, 3243; (g) Zidar N.; Kikelj, D. *Tetrahedron*, **2008**, *64*, 5756; (h) Ballini, R.; Palmieri, A.; Talaq M. A.; Gabrielli, S. *Adv. Synth. Catal.* **2009**, *351*, 2611; (i) Albanese, D.; Donghi, A.; Landini, D.; Lupia, V.; Penso, M. *Green Chem.* **2003**, *5*, 367–369; (j) Albanese, D.; Landini, D.; Lupi, V.; Penso, M. *Adv. Synth. Catal*. **2002**, *344*, 299-302.
25. (a) Nguyen, K. M. H.; Schwendimann, L.; Gressens, P.; Largeron, M. *Org. Biomol. Chem*. **2015**, *13*, 3749-3756 and references therein; (b) Zhang, Q. -Y.; Liu, B. -K.; Chen, W. -Q.; Wu, Q.; Lin, X. -F. *Green Chem*. **2008**, *10*, 972–977.

26. **General procedure for the Synthesis of 2-oxo-benzo[1, 4] oxazines (24a-q, 25a-d and 26-29):** To a solution of the compound **20a-f** (substituted 2-amino phenol; 0.2 mmol) in water was added 0.2 mmol of compound **21a-i** (substituted 2,4-dioxo-4-phynyl butanoic acid), or **22** or **23**; and the reaction mixture was irradiated under ultrasonic sonicator at 80 ˚C temperature for about 75-120 min. (depending upon the substrate employed). The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered off, washed with distilled water (3 × 50 ml) and dried it, which furnished the crude product. The crude product were purified either by recrystallization using EtOAc/Hexane or EtOH; or by flash column chromatography method over silica gel using 9:1 Hexane/ethyl acetate as an eluent which afforded the pure desired 2-oxo-benzo[1,4]oxazines **24a-q**, **25a-d** and **26-29**, respectively in excellent yield (76-98 %).
*Characterization data of representative (Z)-7-nitro-3-(2-oxo-2-phenylethylidene)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**24n**)*:
Yellowish solid; yield: 57.5 mg (89 %), m.p. 240-242 °C; FT-IR (KBr, vmax/cm-1) 3436, 1763, 1622, 1596, 1268; 1H NMR (400 MHz) δ 8.06 - 8.00 (m, 4H), 7.83 – 7.81 (m, 1H), 7.62 (t, J = 7.3 Hz, 1H), 7.54 (t, J = 7.5 Hz, 2H), 6.99 (s, 1H); 13C NMR (100 MHz) 190.7, 156.1, 142.2, 141.1, 139.2, 138.3, 133.6, 131.3, 129.6, 128.0, 121.4, 117.4, 112.6, 96.0; HRMS (ESI) calcd. for $C_{16}H_{10}N_2O_5$ [M+H]+: 311.0590; found 311.0595.

27. **General procedure for the Synthesis of 2-oxo-quinoxaline analogues (31a-b, 32a-b and 33a-b):**To a solution of 0.2 mmol of benzene-1,2-diamine **30a-b** in water was added 0.2 mmol of compound **21a** or **22** or **23**; and the reaction mixture was irradiated under ultrasonic sonicator at 80 ˚C temperature for about 75-120 min. (depending upon the substrate employed). Progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered off, washed with distilled water (3 × 50 ml) and dried it, which furnished the crude product. The crude product were purified either by recrystallization using EtOAc/Hexane or EtOH; which afforded the pure desired 2-oxo-quinoxaline analogues (**31a-b**, **32a-b** and **33a-b**) having excellent yield (80-95 %).
*Characterization data of representative (Z)-3-(2-(anthracen-9-yl)-2-oxoethylidene)-3,4-dihydroquinoxalin-2(1H)-one (**32a**):*
Yellowish solid; yield: 64.6 mg (90 %), m.p. > 250 °C; FT-IR (Neat, vmax/cm-1) 2920, 1671, 1596, 1455, 1131; ^{1}H NMR (400 MHz) δ 11.86 (s, 1H), 8.66 (d, J = 6.0 Hz, 1H), 8.13 – 8.09 (m, 4H), 7.59 – 7.47 (m, 5H), 7.20 – 7.19 (m, 3H), 6.37 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 193.7, 155.1, 144.5, 136.2, 130.5, 128.2, 127.9, 127.3, 126.8, 126.7, 125.9, 125.8, 125.0, 124.9, 124.7, 123.8, 116.3, 96.2; HRMS (ESI) calcd. for $C_{24}H_{16}N_2O_2$ [M+H]+: 365.1212; found 365.1218.

28. **Synthesis of 3-(1H-indol-3-yl)-2H-benzo[b][1,4]oxazin-2-one (35**): To a solution of the compound **20a** (130.8 mg, 1.20 mmol) in water was added 3-Indoleglyoxylic acid **34** (226.9 mg, 1.20 mmol); and the reaction mixture was irradiated under ultrasonic sonicator at 80 ˚C temperature for about 180 min. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered off, washed with distilled water (3 × 50 ml) and dried it, which furnished the crude product. The crude product was further purified by recrystalization using EtOAc/Hexane and EtOH; which afforded the pure desired Cephalandole A **35** having good yield (255.4 mg, 81 %). Yellowish solid; yield: 255 mg (81) %, m.p. 230-232 °C; FT-IR (KBr, vmax/cm-1) 3292, 3053, 2921, 2852, 1713, 1604, 1428, 1151; ^{1}H NMR (400 MHz) δ 11.99 (s, 1H), 8.77 – 8.75 (m, 1H), 8.70 (s, 1H),

7.84 (d, J = 6.4 Hz, 1H), 7.55 – 7.53 (m, 1H), 7.48 – 7.38 (m, 3H), 7.29 – 7.24 (m, 2H); ^{13}C NMR (100 MHz) δ 152.1, 147.9, 144.9, 136.6, 133.8, 131.9, 128.7, 127.7, 126.0, 125.3, 123.1, 122.9, 121.6, 115.9, 112.2, 110.6; HRMS (ESI) calcd. for $C_{16}H_{10}N_2O_2$ $[M+H]^+$: 263.0742; found 263.0749.

Supplementary Material

The supporting information related to this article includes general experimental procedure, copies of ^{1}H and ^{13}C spectral data of all the compounds **24a-q, 25a-d, 26-29**, **31a-b**, **32a-b**, **33a-b** and Cephalandole A **35** can be found at electronic supplementary material section.