Tetrahedron Letters xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Traceless synthetic approach towards oxaza-dicyclopenta[*a*,*h*]naphthalenes under solvent-free condition: a basic alumina-supported green protocol

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ARTICLE INFO

Article history:
Received 24 January 2013
Revised 19 March 2013
Accepted 22 March 2013
Available online xxxx

Keywords:
Oxaza-dicyclopenta[*a*,*h*]naphthalene
Furo[3,2-*h*]quinolinium
1,3-Dipolar cycloaddition
Basic alumina
Green chemistry

ABSTRACT

A novel class of oxaza-dicyclopenta[*a*,*h*]naphthalenes was efficiently constructed from furo[3,2-*h*]quinoliniums through a 1,3-dipolar cycloaddition reaction employing basic alumina as the solid support. The distinguished features of this methodology encompass high yield, minimal reaction time, operational simplicity and general applicability coupled with structural novelty of the products. The intermediate furo[3,2-*h*]quinoliniums were easily derived through a two-step methodology, namely a tandem Sonogashira–alkynylation–cyclization, followed by quaternization of the furo[3,2-*h*]quinoline scaffold.

The conclusion of Human Genome Project (HGP) in 2003 has delivered the DNA-sequence information of a wide variety of genomes ranging from microbial to macro species, which led the chemists to construct newer and more diversified organic scaffolds and the biologists to explore these libraries on DNA and protein targets.[1] Among several such chemical scaffolds, heterocyclic compounds have always held the centre stage because more than half of the bioactive natural products contain differently modified mono or polynuclear heterocyclic cores as an essential part of their skeleton.[2] Among them benzo[*b*]furans and indolizines constitute crucial structural components of a wide variety of bioactive drug candidates of both synthetic and natural origin.[3] They are well known for their antitumor,[4] antifungal,[5] antiviral,[6] antibacterial,[7] antileishmanial,[8] analgesic,[9] antioxidant,[10] antiinflammatory[11] and agrochemical[12] properties. Apart from these, benzo[*b*]furans display protein phosphatase 1B inhibitory[13] and 5-lipoxygenase (5-LO) inhibitory properties[14] as well as 5-HT_2 and 5-HT_3 antagonist activity,[15] while indolizines function as aromatase inhibitor,[16] calcium entry blocker[17] and histamine H_3 receptor antagonists.[18] From pharmaceutical point of view these are the characteristics of potential drug candidates for the treatment of cancer, cardiovascular diseases, diabetes, migraines, dementia and anxiety.[4a,15] Therefore, construction of newer and more complex chemical entities featuring benzo[*b*]furan or indolizine cores in their skeleton and screening of these libraries for the identification of newer lead molecules has garnered immense importance. We contemplated that combining the two units in one composite structure as shown in Figure 1 may lead to novel biologically active entities, for example, oxaza-dicyclopenta[*a*,*h*]naphthalenes. A survey of the literature brought out to our surprise that no synthetic attempts have been made on this ring type, nor are there any reports of their bio-evaluation studies. Thus, in continuation of our decade long investigations on the development of structurally unique bioactive heterocyclic compounds,[5b,19] we decided to take up the synthesis of a new class of chemical species having oxaza-dicyclopenta[*a*,*h*]naphthalene as the core moiety. The synthetic scheme was planned to utilize furo[3,2-*h*]quinoliniums as the stepping stone towards the final compounds. We also tried to focus our attention on the application of green tools from our recently developed green tool box[20] in this task, because development of environmentally-friendly modifications of hazardous chemical conversions is increasingly gaining importance due to the rapidly growing global environmental legislation now-a-days.[21] In this report, we disclose the results of our recent synthetic studies on the construction of differently substituted oxaza-dicyclopenta[*a*,*h*]naphthalenes under solvent-free solid supported condition.

Our plans to reach the targeted composites involved a two phase synthetic effort, which began with the formation of the desired cyclization precursor. Initially, the dual function of basic alumina as a base as well as solid support was efficiently harnessed for our recently developed tandem Sonogashira cross-coupling-cyclization protocol, which eventually yielded the furo[3,2-*h*]quinolines (**3a**–**c**) from 5-chloro-8-hydroxyquinoline (**1**) and appropri-

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0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.03.095

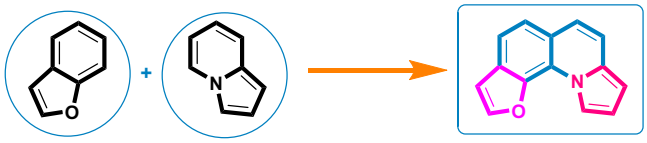


Figure 1. Hypothetical composite of benzo[*b*]furan and indolizine cores.

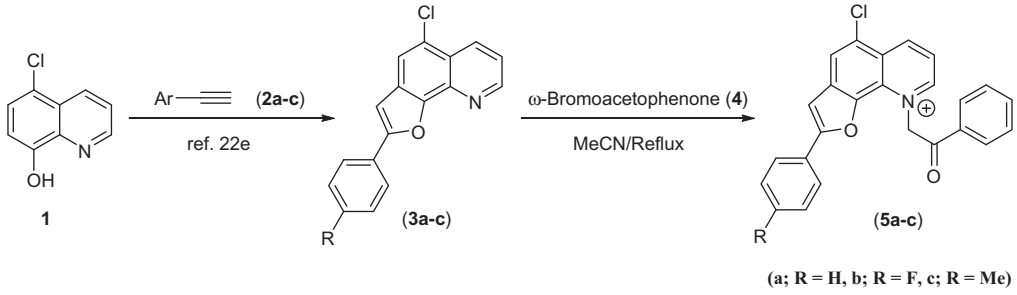
ate terminal alkynes (**2a**–**c**).[20d] Quaternization of the quinoline motif in the next step of this strategy was then satisfactorily done with ω-bromo-acetophenone (**4**) under refluxing condition in acetonitrile (Scheme 1), which furnished the cyclization precursors (**5a**–**c**) in reasonable yield (Table 1).

With these furo[3,2-*h*]quinoliniums in our possession, we moved towards the final phase for the construction of our targeted heterocycles. Initial efforts were directed towards optimization reactions using furo[3,2-*h*]quinolinium **5a** and diethyl acetylene dicarboxylate **6a** as the reaction partners in the presence of different bases and refluxing in different solvents. As brought out by the entries in Table 2, the reactions employing variable combinations of solvents and bases, however, ended up with discouraging results producing only 10–15% yield of the desired product (**7a**). Even our recently developed resin-assisted route[5b] also failed to improve the yield beyond 31% (entry 5). Thus we opted for a newer protocol and among the plenty of possible tools, the combination of basic alumina with microwave irradiation appealed to us most. It is a widely used heterogeneous catalyst and has gained prominence in several areas of organic synthesis.[22]

An encouraging result with a substantial improvement in the product yield (57%) was obtained in the initial attempt for carrying out the reaction (1,3-dipolar cycloaddition) using basic alumina at 80 °C (180 W); this could eventually be raised to 93% at 90 °C (180 W) (entry 7). In order to establish the benefits of employing microwave as the heating source, the same reaction was performed on an oil bath for 12 h at 90 °C to obtain the product to the extent of 43% only, which unambiguously proved the superiority of microwave irradiation. The products and their yield of formation are summarized in Table 3.

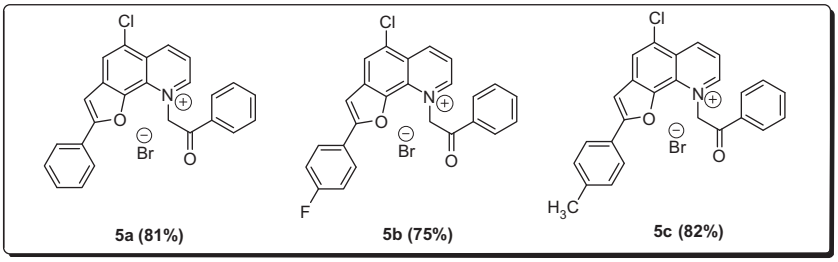
Finally, we performed an investigation on the reusability of this solid support to determine its importance for both academic and industrial application. It was observed that the support material becomes almost as active as a fresh sample after proper washing with water and acetone followed by calcination at 150 °C, and can be recycled 3–4 times without affecting its activity noticeably (Fig. 2).

The mechanism of the cycloaddition is expected to proceed with an initial deprotonation of **5b** by basic alumina, thereby generating 1,3-dipole **I**, which immediately attacks the dipolarophile **6c** for a [3+2] cycloaddition reaction followed by aromatization, leading to the product **7g** (Scheme 2). Structure of **7g** was preliminarily confirmed by its ^{1}H NMR analysis.[24] Disappearance of peaks for the methylene hydrogens (δ = 6.99) and the ring hydrogen (δ = 9.66) α to the quaternary ammonium centre of **5b**, coupled with the appearance of a newly developed singlet proton at δ = 6.97 in the spectrum of **7g**, assigned to the only available proton of the newly formed fused pyrrole unit, signalled the success of the reaction. Besides, a triplet at δ = 1.44 and a quartet at δ = 4.43 were assigned to the ethyl group of the carbethoxy group. There were fourteen other singlets and multiplets in the aromatic region (δ = 6.66–8.41), assigned to the aromatic protons of **7g**. These assignments were further supported by its ^{13}C NMR spectra. Signals for the methylene (δ = 67.1 in **5b**) and the methine carbon (δ = 145.0 in **5b**) α to the quaternary ammonium centre were absent, being replaced by peaks for quaternary carbons at δ = 125.1 and 139.3, respectively. Signals attributable to one additional quaternary carbon centre (δ = 107.6), a methine carbon (δ = 127.0) and a methyl peak in the aliphatic region (δ = 14.5) were also in accord with the proposed structure of the cycloadduct **7g**. Eighteen other



Scheme 1. Synthesis of cyclization precursors.

Table 1
Synthesis of cyclization precursor's **5a**–**c**[a,b]



[a]All the reactions were performed in acetonitrile under refluxing condition.
[b]Isolated yield.

Table 2
Optimization of conditions of reaction between **5a** and **6a**

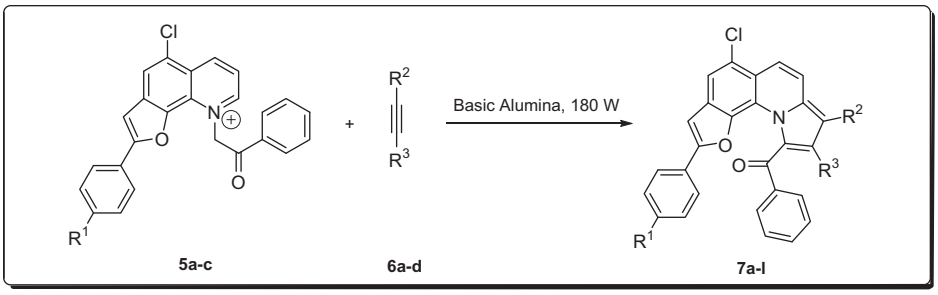
Entry	Base	Solvent	Time (h)	Temp (°C)	Yield[a] (%)
1	DBU	DCM	10	Reflux	15
2	Na_2CO_3	DCM	10	Reflux	11
3	Na_2CO_3	Methanol	12	Reflux	11
4	Cs_2CO_3	Acetonitrile	12	Reflux	10
5	Amberlite resin	Water/$CHCl_3$	12	rt	31
6	Basic alumina	—	5 min	80	57[b]
7	Basic alumina	—	5 min	90	93[b]

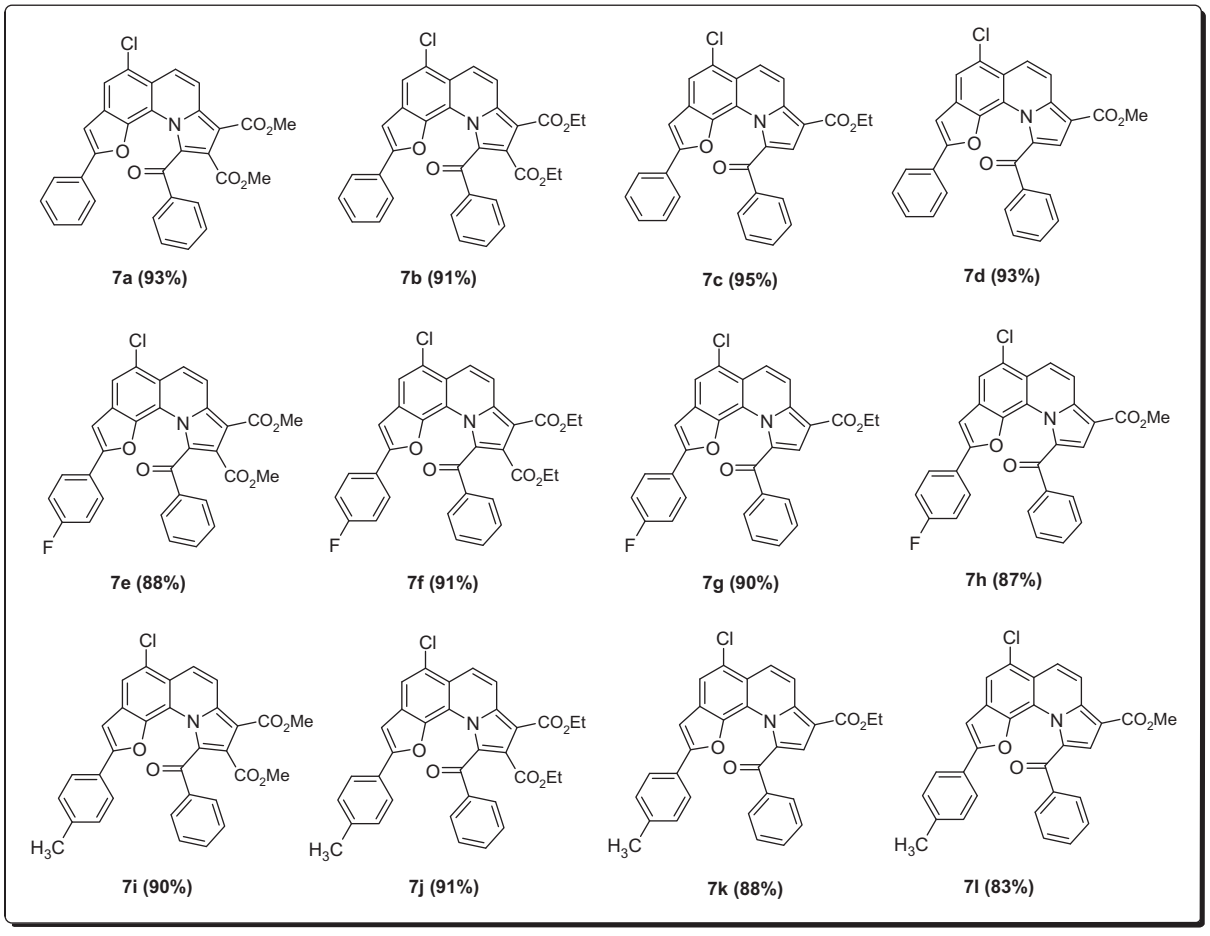
[a] Isolated yield.
[b] The reactions were performed under microwave irradiation at 180 W.

signals in the ^{13}C NMR spectra were assigned to the remaining methine and quaternary carbon centres. In addition to the NMR studies, the HRMS analysis of **7g** also agrees with the proposed skeleton. However, the most convincing evidence in this regard was obtained from the single crystal X-ray crystallographic analysis of **7g**, which explicitly proved its structure, as obvious from the ORTEP diagram shown in Figure 3.

In conclusion, we have explored the use of basic alumina as a reactive solid support system for the synthesis of some oxaza-dicyclopenta[*a*,*h*]naphthalene analogues through a 1,3-dipolar cyclo-

Table 3
Synthesis of oxaza-dicyclopenta[*a*,*h*]naphthalene analogues[a,b]





[a]All the reactions were performed under microwave irradiation (180 W) at 90 °C.
[b]Isolated yield.

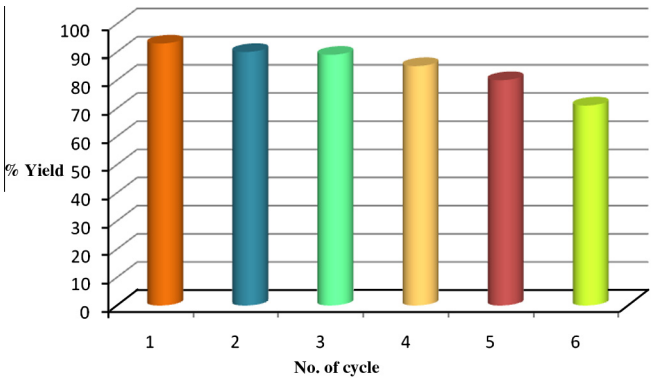
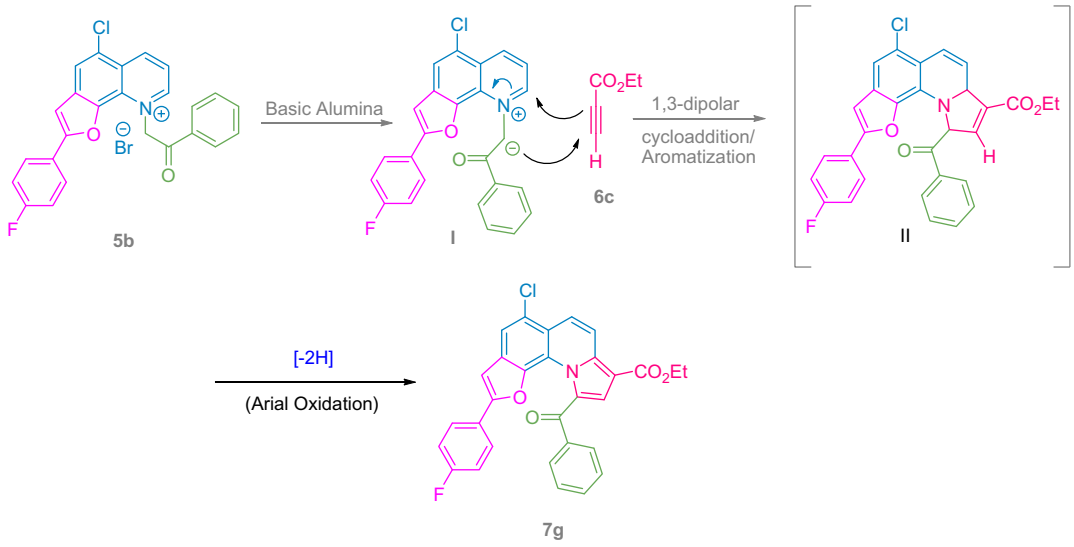


Figure 2. Reusability of the basic alumina tested using **5a** and **6a**. The reactions were performed with **5a** (3.3 mmol) and **6a** (3.3 mmol), using 400 mg basic alumina at 90 °C for 5 min.[23]

addition reaction in solvent-free media under microwave irradiation. The easy availability and reusability of the solid support, elimination of the use of any acid or solvent, cost-effectiveness of the process, operational simplicity and the use of environmentally benign techniques make it an important green methodology. Furthermore, a detailed study on the DNA-intercalation properties and cytotoxic activities of both furo[3,2-*h*]quinoliniums and oxaza-dicyclopenta[*a*,*h*]naphthalene analogues is currently under investigation in our laboratory and will be reported in due course. To the best of our knowledge, this is the first report of basic alumina-supported oxaza-dicyclopenta[*a*,*h*]naphthalene synthesis.

Acknowledgments

We would like to thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for financial support in the form of fellowships to R.P., S.M., A.M., and A.H. We are indebted to Mr. E. Pad-



Scheme 2. Plausible mechanistic pathway for the basic alumina supported synthesis of oxaza-dicyclopenta[*a*,*h*]naphthalene analogues.

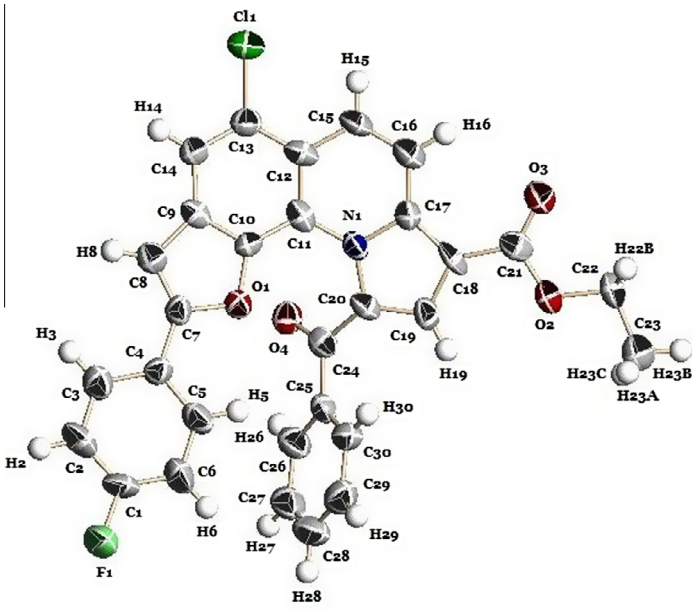


Figure 3. ORTEP representation of compound **7g**, the displacement ellipsoid is drawn at a probability of 50%.

manaban and Mr. K. Sarkar for NMR and mass spectral analysis and also to Dr. B. Achari, Emeritus Scientist, CSIR, for critical suggestions and encouragement.

Supplementary data

Supplementary data (copies of ^{1}H NMR and ^{13}C NMR spectra of all the products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.095. Crystallographic data in CIF format are available free of charge via the Internet at CCDC 902797. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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23. *General procedure for the synthesis of oxaza-dicyclopenta[a,h]naphthalene analogues (**7a–l**)*: 3.3 mmol furo[3,2-*h*]quinolinium derivatives (**5a–c**) and 3.3 mmol dialkyl acetylene diacetates or monoalkyl acetylene monoacetates (**6a–d**) were placed in a RB flask (25 ml.) and dissolved in a minimum amount of chloroform. Basic alumina (0.4 g) was then added to the solution and the organic solvent was then evaporated to dryness under reduced pressure. After fitting the flask with a septum the mixture was subjected to irradiation in a microwave reactor (CEM, Discover, USA) at 90 °C (180 W) for appropriate amount of time (as monitored by TLC). After completion of the reaction the reaction mixture was cooled and chloroform was added to it and the slurry was stirred at room temperature for 10 min. The mixture was then filtered through a sintered glass funnel. The filtrate was then evaporated to dryness under reduced pressure and the residue was purified by flash chromatography to isolate the product (**7a–l**). In the recycling experiment the residue, obtained after vacuum filtration of the reaction mixture, was washed with alkaline water and acetone (2–3 times) and subjected to calcination at 150 °C.
24. *Spectral data of representative compounds: (a) 10-Benzoyl-5-chloro-2-phenyl-1-oxa-10a-aza-dicyclopenta[a,h]naphthalene-8,9-dicarboxylic acid dimethyl ester (**7a**)*: Brown solid. 93% yield; mp 230–232 °C; R_f (20% ethyl acetate/hexane) 0.35; IR (KBr, ν_{max}): 2920, 2851, 1681, 1566, 1457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.51 (s, 3H), 3.94 (s, 3H), 7.00 (s, 1H),7.10 (m, 3H), 7.21 (m, 1H), 7.29 (s, 1H), 7.41 (m, 2H), 7.59 (m, 1H), 7.78 (s, 1H), 7.93 (m, 2H), 8.23 (d, J = 9.9 Hz, 1H), 8.39 (d, J = 9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.1 (CH_3), 52.2 (CH_3), 102.1 (CH), 105.5 (C), 117.3 (CH), 119.5 (CH), 120.8 (C), 121.6 (C), 125.5 (CH),125.6 (2CH), 127.6 (2CH), 128.5 (2CH), 128.6 (C), 128.7 (2CH), 128.8 (C), 129.3 (CH), 130.0 (C), 130.1 (2CH), 130.9 (C), 133.5 (CH), 137.6 (C), 137.8 (C), 142.0 (C), 158.1 (C), 163.8 (C), 166.0 (C), 184.7 (C); HRMS (ESI) m/z calcd for $C_{31}H_{20}ClNO_6$: $[M+Na]^+$ 560.0871; found: 560.0879. *(b) 10-Benzoyl-5-chloro-2-phenyl-1-oxa-10a-aza-dicyclopenta[a,h]naphthalene-8,9-dicarboxylic acid diethyl ester (**7b**)*: Brown solid. 91% yield; mp 231–232 °C; R_f (20% ethyl acetate/hexane) 0.35; IR (KBr, ν_{max}): 2921, 2854, 1690, 1569, 1450 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.11 (m, 3H), 1.40 (m, 3H), 3.83 (m, 2H), 4.40 (m, 2H), 6.99 (s, 1H), 7.09 (t, J = 7.8 Hz, 2H), 7.21 (m, 3H), 7.43 (t, J = 7.8 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.76 (m, 1H), 7.98 (m, 2H), 8.23 (d, J = 9.6 Hz, 1H), 8.42 (d, J = 9.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.7 (CH_3), 14.3 (CH_3), 60.7 (CH_2), 61.8 (CH_2), 101.9 (CH), 105.4 (C), 117.1 (CH), 119.2 (CH), 120.7 (C), 121.5 (), 125.1 (CH), 125.4 (2 CH), 127.3 (C), 128.2 (C), 128.3 (2 CH), 128.5 (2CH), 128.6 (C), 129.0 (CH), 129.9 (C), 130.1 (2 CH), 130.6 (C), 133.3 (CH), 137.5 (C), 137.8 (C), 141.8 (C), 157.7 (C), 163.0 (C), 165.4 (C), 184.5 (C); HRMS (ESI) m/z calcd for $C_{33}H_{24}ClNO_6$: $[M+Na]^+$ 588.1184; found: 588.1172. *(c) 10-Benzoyl-5-chloro-2-(4-fluoro-phenyl)-1-oxa-10a-aza-dicyclopenta[a,h]naphthale-ne-8-carboxylic acid ethyl ester (**7g**)*: Brown solid. 90% yield; mp 246–248 °C; R_f (20% ethyl acetate/hexane) 0.35; IR (KBr, ν_{max}): 2921, 2851, 1690, 1576, 1457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, J = 7.2 Hz, 3H), 4.43 (m, 2H), 6.66 (t, J = 8.7 Hz, 2H), 6.97 (s, 1H), 7.17 (m, 2H), 7.63 (t, J = 7.5 Hz, 2H), 7.78 (m, 3H), 8.25 (m, 3H), 8.41 (d, J = 9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5 (CH_3), 60.3 (CH_2), 101.3 (CH), 107.6 (C), 115.4 (2CH), 115.6 (CH), 117.0 (CH), 118.8 (CH), 120.4 (C), 121.9 (C), 124.9 (CH), 125.1 (C), 127.0 (CH), 127.1 (CH), 127.2 (C), 128.7 (2 CH), 128.7 (C), 130.3 (C), 130.4 (2 CH), 130.5 (C), 133.2 (CH), 137.4 (C), 139.3 (C), 142.0 (C), 156.4 (C), 164.1 (C), 183.4 (C); HRMS (ESI) m/z calcd for $C_{30}H_{19}ClFNO_4$: $[M+Na]^+$ 534.0879; found: 534.0893.