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DESIGN AND SYNTHESIS OF PENTACYCLOUNDECANE CAGE COMPOUND CONTAINING OXAZOLE MOIETY

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Abstract – Here, we have established a new and simple synthetic approach to the pentacycloundecane containing cage oxazole unit in four steps. The synthesis begun with a cheap and readily available materials such as 2,5-dimethoxybenzaldehyde and *endo*-dicyclopentadiene. This approach relies on Van Leusen oxazole synthesis and [2+2] photocycloaddition as key steps. To the best of our knowledge, this is the first example of Cookson's dione containing oxazole ring system. Some of these oxazole motifs are useful in bioorganic chemistry and our results are likely to draw the attention of medicinal chemists

Cage hydrocarbons are considered as a privileged scaffolds for novel drug design and pharmaceutical applications. The medicinal properties of these molecules and their molecular architecture, conformational rigidity, and extended cage size, propeller chirality along with lipophilic character merit their attention.[1] Hydrocarbon moieties help the transport of drugs across the cell membranes and increase their affinity for lipophilic regions in the receptor molecules. Therefore, drugs containing cage frameworks provide an additional advantage in longevity of drug action, enhanced drug effectiveness, improve the speed of action and receptor specificity along with the antibacterial activity, anabolic action, analgesic activity and antiviral activity.[2] Several pentacycloundecane (PCUD) cage frameworks containing heterocyclic motifs are found to be useful in the various fields such as supramolecular chemistry, medicinal chemistry as well as asymmetric catalysis.[3-5] Most of the pharmaceutical intermediates comprise of heterocycles in their molecular structures and these are responsible for their biological activity.[6] In 2009, Govender *et al*. have synthesized the fourteen PCUD containing cage heterocycles (tetra-amine compounds) and those are screened them against two TB strains, H37Rv, and XDR 194 as well as they displayed excellent anti-TB activity against *M-tuberculosis* H37Rv.[7] For example, different varieties of PCUD containing cage heterocyclic frameworks **1-4** (Figure 1) are useful in medicinal and pharmaceutical applications. These heterocycles display an interesting activities against

tuberculosis, anti-parkinson activity, and neurodegenerative diseases.[8]

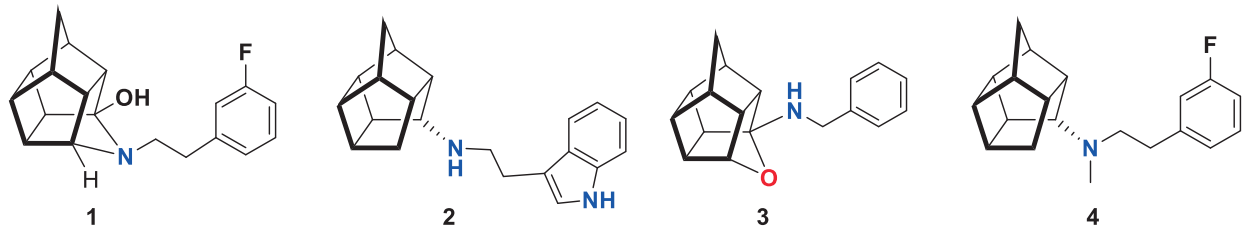


Figure 1. Biologically important cage heterocycles containing PCUD framework

Oxazoles are prevalent class of heteroaromatic entities and they are useful for various applications. These includes: agrochemicals, materials, diverse natural products and modern pharmaceutical ingredients. These five-membered hetero aromatic species containing nitrogen and oxygen atoms bind with a different types of enzymes and receptors by non-covalent interactions and exhibit biological activities.[9,10] Several chemists made significant synthetic effort during the last few decades due to their broad range of activities such as antifungal, antiviral, antitubercular, anticancer, antidiabetic, antidepressant, and antibacterial as well as potent anti-oxidant and anti-inflammatory activities.[11] Some of the oxazole scaffolds serve as a key synthons for new chemical entities (NCE) in medicinal and pharmaceutical industry (Figure 2). [12]

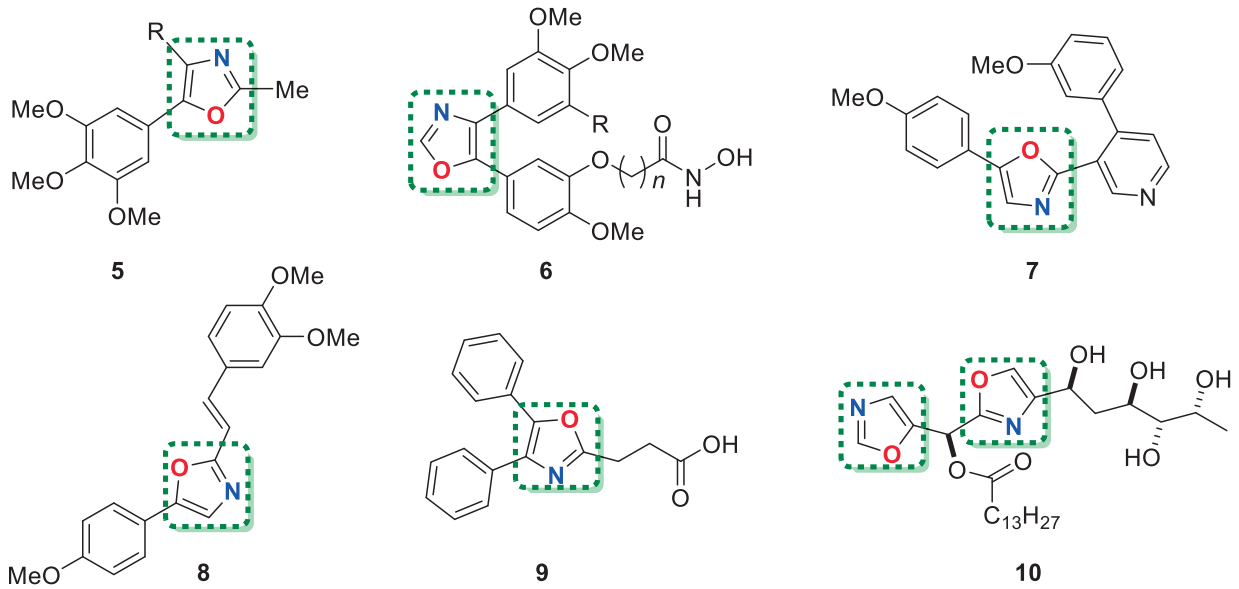
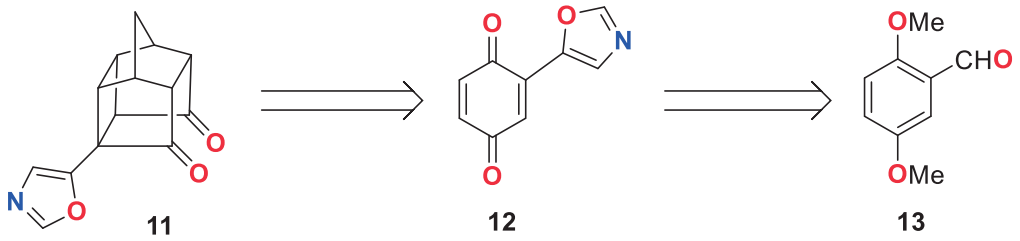


Figure 2. Examples of biologically active, medicinal, and natural product containing oxazole moieties

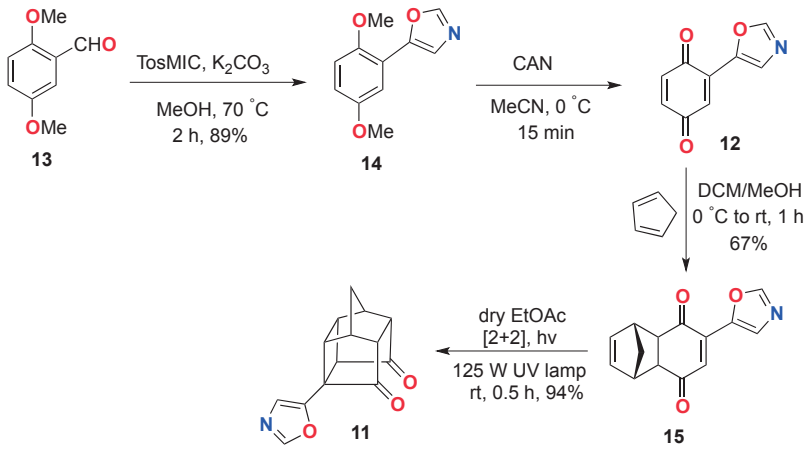
In addition, some of the oxazole frameworks are emerged as an efficient ligands in asymmetric catalysis, building blocks in polymer syntheses, peptidomimetics and fluorescent organic dyes.[13] Compounds that are shown in Figure 2, play a significant role as antitubulin agents, histone deacetylase (HDAC) inhibitors, anticancer agents (PC-046) and bioactive natural products.[14] For example, oxazole scaffold **9** (oxaprozin) serve as a non-narcotic, non-steroidal anti-inflammatory (NSAID) drug used for the treatment of rheumatoid arthritis.[15] Bengazole A **10** (bis-oxazole) exhibits antihelminthic activity against *Nippostrongylus braziliensis* and acts as a potent antifungal agent.[16] Moreover, the synthesis and study of these heterocyclic scaffolds with completely modified new structural skeletons are become worthy for further exploration. The modification of oxazole systems may improve their enhanced drug resistances, change in mechanism of actions and increase in prominent biological activities as a lead compound in medicinal and pharmaceutical drug discovery. [17]

In recent years, we have developed a new synthetic methodology to a variety of carbocyclic cage compounds containing heterocycles such as cage propellanes, oxa-D_3 trishomocubanes, polycyclic bis-indoles, and bis-annulated oxa-cage propellanes using cycloadditions, olefin-metathesis, and rearrangement approaches.[18] In view of our interest to construct biologically active cage frameworks having heterocyclic moiety in their skeleton, here we conceived a short synthetic sequence to PCUD containing cage oxazole under Van Leusen reaction conditions (Scheme 1).



Scheme 1. Retrosynthetic path to the cage oxazole **11**

Based on the retrosynthetic plan depicted in Scheme 1, the PCUD system containing oxazole moiety **11** would be assembled starting with quinone derivative **12** via Diels–Alder (DA) sequence[19] followed by intramolecular [2+2] photocycloaddition.[20] The quinone **12** may be assembled from an inexpensive and readily available 2,5-dimethoxybenzaldehyde **13** involving Van Leusen oxazole procedures followed by CAN oxidation (Scheme 1).



Scheme 2. Synthesis of PCUD system **11** containing oxazole

From retrosynthetic route shown in Scheme 1, our journey towards the synthesis of the target PCUD cage compound **11** commences with the commercially accessible 2,5-dimethoxybenzaldehyde **13** (Scheme 2). Initially, the aldehyde **13** was reacted with TOSMIC[21] in the presence of K_2CO_3 in methanol at reflux conditions to give the required dimethoxyoxazole **14** in 89% yield. Further, oxidation of the dimethoxy-oxazole **14** was performed with CAN in acetonitrile/water at 0 °C afforded the quinone derivative **12** a useful dienophile suitable for DA sequence. Later, thermal [4+2] cycloaddition of the quinone **12** with a freshly cracked 1,3-cyclopentadiene at 0 °C in DCM/MeOH delivered the DA cycloadduct **15** in 67% yield. Finally, the *endo*-DA adduct **15** was subjected to intramolecular [2+2] photocycloaddition in dry EtOAc under nitrogen by the irradiation with 125 W Hg lamp for 90 min to produce the cage dione **11** containing oxazole moiety in excellent yield (Scheme 2). The structure of the cage oxazole **11** was fully characterized with the ^{1}H NMR, ^{13}C NMR, DEPT-135 NMR, ^{13}C-APT, and finally supported by the HRMS data.

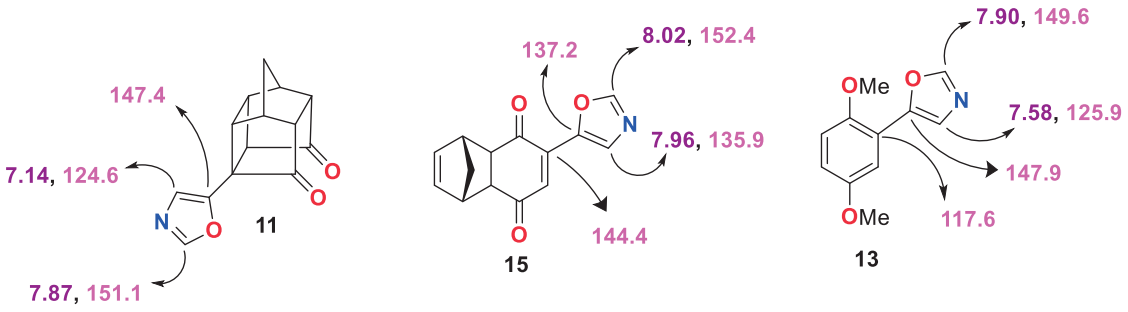


Figure 3. Correlation of ^{1}H and ^{13}C NMR value (s) of different oxazole derivatives

The ^{1}H NMR spectrum of cage oxazole **11** clearly specifies the presence of two singlets (two olefinic protons) at δ 7.87 (1H) indicates neighboring proton of nitrogen and oxygen and δ 7.14 (1H) represents adjacent proton of quaternary carbon for the oxazole of caged system (Figure 3). Furthermore, the ^{13}C

NMR spectrum of **11** revealed the three characteristic peaks at δ 151.1, 147.4, and 124.6 ppm indicates the presence of oxazole ring of cage system. These ^{13}C values represents the –CH and quaternary carbon of the oxazole contiguous to N & O atoms (Figure 3).

In summary, we have successfully synthesized the oxazole containing cage framework. The PCUD containing cage oxazole compound was synthesized by the combination of Van Leusen reaction and [2+2] photocycloaddition. It is worthwhile to remark that the oxazole bearing PCUD cage frameworks may become a valuable candidates for applications in medicinal/pharmaceutical and drug delivery. Moreover, cage compounds are also valuable synthons in polyquinane chemistry.[22]

EXPERIMENTAL

General Experimental Details

Essential reagents, chemicals, and necessary solvents are used as such directly obtained from commercial suppliers. Thin-layer chromatography (TLC) plates were made on 10 × 5 glass plates layered with commercial-grade Acme's silica gel (GF-254) containing 13% $CaSO_4$ which acts as a binder. Reaction progress was analyzed by TLC with a suitable solvent systems (EtOAc/Pet ether) and observation was done by UV and iodine spray. Moisture sensitive reactions were achieved by oven-dried glassware under nitrogen/argon atmosphere by using syringe-septum techniques. Column purification was performed with 100-200 mesh silica gel with suitable solvent systems. Dry CH_2Cl_2 were distilled over calcium hydride (CaH_2) and EtOAc was dried with anhydrous K_2CO_3.

All IR samples were recorded with DCM and chloroform as solvents on Nicolet Impact-400 FTIR spectrometer. NMR spectra (^1H, ^{13}C and DEPT 135) have been recorded on 400 and 500 MHz spectrometers (Bruker) with $CDCl_3$ solvent and chemical shifts (δ ppm) are reported relative to internal standard such as TMS. The *J* values (coupling constants) are given Hz. Mass spectra (HRMS) have been recorded under positive ion electrospray ionization (ESI, Q-TOF) mode.

Experimental procedures and characterization data

5-(2,5-Dimethoxyphenyl)oxazole (14)

To a stirred solution of mono-aldehyde such as **13** (1.0 equiv, 1 g, 6.0 mmol) were added to a TosMIC (1.1 equiv, 1.2 g, 6.6 mmol) and K_2CO_3 (4 equiv, 3.3 g, 24.0 mmol) in MeOH (25 mL). Later on, the resulting reaction mixture was heated to 70 °C for 2 h. At the end of the reaction which was monitored by TLC, MeOH was removed under vacuo and the crude reaction mixture was purified by column chromatography with 100-200 mesh silica gel column. Elution of the silica gel column with 15% EtOAc in petroleum ether gave the desired dimethoxyoxazole **14** in pure form.

Colourless crystalline solid; Yield: 1.1 g (89%); Mp 69-71 °C; IR (neat, cm^{-1}): υ_{max} = 3128, 3003, 2955,

2898, 2837, 1576, 1505, 1457, 1440, 1403, 1330, 1280, 1271, 1246, 1222, 1183, 1151, 1117, 1092, 1049, 1022, 953, 859, 831, 807, 643, 577; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.90 (s, 1H), 7.58 (s, 1H), 7.33 (d, J = 2.9 Hz, 1H), 6.91-6.90 (m, 1H), 6.86-6.83 (m, 1H), 3.91 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 153.8, 150.2, 149.6, 147.9, 125.9, 117.6, 114.6, 112.2, 111.4, 56.09, 56.02; HRMS (ESI, Q-ToF): *m/z* calcd for $C_{11}H_{11}NO_3$ $[M+H]^+$ 206.0812, found: 206.0817.

2-(Oxazol-5-yl)cyclohexa-2,5-diene-1,4-dione (12)

Ceric ammonium nitrate (6.1 mmol, 2.5 equiv) dissolved in 20 mL of ice-cold water was added to a stirred solution of oxazole **14** (500 mg, 2.4 mmol, 1 equiv) in MeCN (10 mL) over a period of 10 min in a dropwise manner. Further, the reaction mixture was stirred at 0 °C for another 10 min. Further, the reaction mixture was diluted with water and extracted with dichloromethane (DCM). The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained crude quinone product **12** (350 mg) was subjected to the next step (DA reaction) immediately without the purification due to its instability at room temperature for a long time.

Synthesis of DA Adduct 15

Freshly cracked cyclopentadiene (3.42 mmol, 3 equiv) was added to a stirred solution of quinone **12** (200 mg, 1.14 mmol, 1 equiv) in DCM/MeOH (15 mL) under 0 to -5 °C. Next, the reaction was stirred at room temperature for 1 h and completion of the reaction was monitored by TLC, the solvent was removed under vacuo and the crude residue was subjected to silica gel (100-200 mesh) column chromatography by using 30% EtOAc in petroleum ether as an eluent to afford the DA adduct **15** (*endo*).

Thick yellow liquid; Yield: 185 mg (67%); IR (neat, cm^{-1}): υ_{max} = 2924, 2853, 1677, 1496, 1464, 1264, 1225, 1177, 707; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.02 (s, 1H), 7.96 (s, 1H), 6.94 (s, 1H), 6.11-6.05 (m, 2H), 3.58 (d, J = 16.2 Hz, 2H), 3.37 (dd, J = 8.5, 4.0 Hz, 1H), 3.28 (dd, J = 8.5, 4.0 Hz, 1H), 1.57 (d, J = 8.7 Hz, 1H), 1.47 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 198.8, 196.1, 152.4, 144.4, 137.2, 135.9, 135.2, 134.1, 133.2, 49.5, 49.4, 49.1, 49.0, 48.8; HRMS (ESI, Q-ToF): *m/z* calcd for $C_{14}H_{11}NO_3$ $[M+Na]^+$ 264.0631, found: 264.0634.

Synthesis of Cage Oxazole 11

The DA adduct **15** (150 mg, 0.62 mmol) was dissolved in anhydrous EtOAc (300 mL) and irradiated for 30 min in a pyrex immersion well by using 125 W UV lamp (home-made) under nitrogen atmosphere at room temperature. The progress of the reaction was monitored by TLC, the solvent was evaporated under reduced pressure and further purification of the crude mixture by column chromatography on 100-200 mesh silica gel using 40% EtOAc in petroleum ether as an eluent which delivers the pure oxazole

containing cage compound **11**.

Colourless viscous liquid; Yield: 140 mg (94%); IR (neat, cm^{-1}): υ_{max} = 2979, 2869, 1739, 1508, 1454, 1270, 1212, 1177, 1120, 1086, 1049, 988, 922, 852, 736, 702, 645; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.87 (s, 1H), 7.14 (s, 1H), 3.40-3.31 (m, 2H), 3.04 (dt, *J* = 17.2, 4.2 Hz, 1H), 2.97-2.95 (m, 1H), 2.92-2.89 (m, 1H), 2.85-2.82 (m, 1H), 2.13 (d, *J* = 11.5 Hz, 1H), 1.98 (d, *J* = 11.5 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 209.8, 206.9, 151.1, 147.4, 124.6, 55.18, 55.14, 49.6, 48.8, 45.5, 44.3, 44.0, 40.7, 37.5; HRMS (ESI, Q-ToF): *m/z* calcd for $C_{14}H_{11}NO_3$ $[M+Na]^+$ 264.0631, found: 264.0637.

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