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Utility of Cyclododecanone as Synthon to Synthesize Fused Heterocycles

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Abstract Ethyl 2-oxocyclododecanecarboxylate (**1**), and 2-(hydroxyl-methylene)cyclododecanone (**7**) were used as key intermediates for synthesis of macrocyclic systems incorporating either fused or exocyclic nitrogen heterocycles of different ring sizes. Ring enlargement was also implemented.

Keywords Cyclododecanone, B-Ketoesters, Pyrazolones, Enaminoketones, Fused Heterocycles

1. Introduction

β-Ketoesters are readily available synthetic building blocks of high importance in organic synthesis. They are used for construction of diverse heterocyclic ring systems belonging to different classes of simple and fused heterocycles[1,2]. Their copper complexes are valuable catalysts in many organic transformations[3,4]. A few of bicyclic or binary systems, including seven-, six- and five-membered heterocycles fused with a dodecamethylene ring, have been synthesized based on cyclododecanone[5,6]. Among these, compounds possessing biological activity and natural compounds, *e.g.,* muscopyridines, have been found[7]. Zoorob *et al*[8], has been exploring the literature survey of cyclododecanone compounds including their reactivity features. In the present work, we aimed to synthesize a number of heterocycles fused or binary with a dodecamethylene ring starting from cyclododecanone derivatives.

2. Results and Discussion

Pyrazolones have gained importance as drug substances in pharmaceutical industry in view of their biological importance. For instance, pyrazolones possess antimicrobial, antifungal[9], antimycobacterial[10], antibacterial[11], anti-inflammatory[12], antitumor[13], gastric secretion stimulatory[14], antidepressant[15] and anti-filarial activities[16]. They also serve as precursors for dyes, pigments, pesticides and chelating agents[17]. They also have many industrial applications. Thus, pyrazolone **2** was synthesized by condensation of ethyl 2-oxocyclodode- canecarboxylate (**1**) with phenylhydrazine. The structure of **2** was supported by IR, ^{1}H NMR and mass spectra. Its IR spectrum displays a strong absorption at υ = 3277 (NH) and at 1696 cm^{-1} (γ-lactam carbonyl group). Its ^{1}H NMR spectrum revealed that it may exist as a mixture of two tautomers **2a** and **2b**, where it displays a singlet signal for 1H at δ 6.4 ppm indicating NH group (structure **2b**) and a multiplet signal for 1H at δ 2.65 ppm indicating the proton at C_4 (structure **2a**) besides the rest of bands corresponding to 5 aromatic protons at δ 7.1-7.8 ppm and 16 aliphatic protons at 1.1-1.5[18].

Also, the isoxazolone **3** was simply synthesized by reaction of the ketoester **1** and hydroxylamine hydrochloride in refluxing methanol containing pyridine. The structure of **3** was attested by IR, ^{1}H NMR and MS spectra. Its ^{1}H NMR spectrum displays the main important signals that correspond to the proton adjacent to the carbonyl group as a multiplet at δ 2.55 (1H), besides the other twenty protons as quartet at δ 2.35 (2H) and multiplet at δ 1.1-1.7 ppm (18H). Moreover, the mass spectrum of **3** was in a good agreement with its structure where it displays a molecular ion peak with *m/z* 223 (24.3%).

Furthermore, aminopyrimidines are important biologically active agents such as antiplatelet[19] and as VEGF-R2 inhibitors[20] and they are also important synthetic intermediates for fused heterocycles[21,22]. This enthused us to synthesize 2-amino-5,6,7,8,9,10,11,12,13,14-decahydro cyc lododeca[*d*]pyrimidin-4(3*H*)-one (**4**) *via* treatment a mixture of the ketoester **1** and guanidine nitrate with sodium ethoxide in ethanol. The ^{1}H NMR of **4** spectrum displays a signal corresponding to eight methylene groups as multiplet at δ 1.1-1.6 (16H), a triplet signal at δ 2.25 (4H) corresponding to two methylenes neighboring to the double bond, a singlet signal at δ 6.5 ppm (2H) corresponding to (NH_2) group and a singlet signal at δ 8.08 ppm (1H) corresponding to (NH) group.

Furthermore, 2*H*-chromene-2-ones (coumarines) continue to be investigated because of their importance to medicinal chemists due to a variety of biological activities. Associated with the coumarine scaffold are antibacterial, antiviral,

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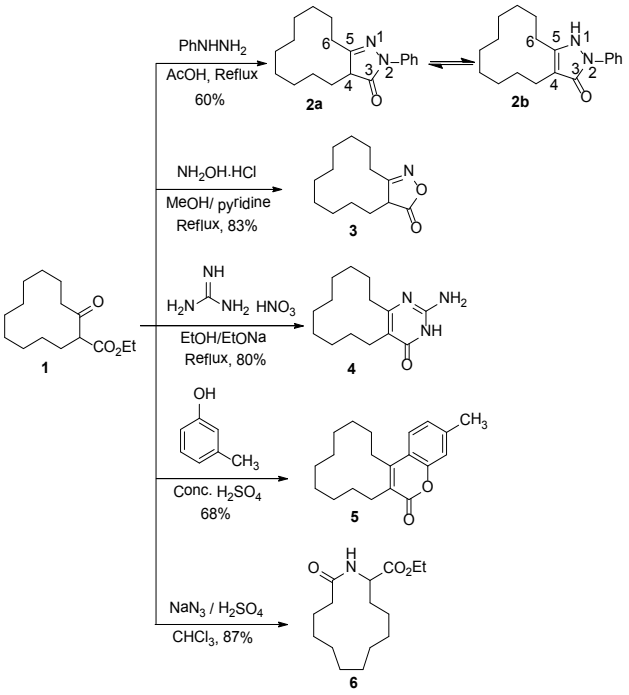
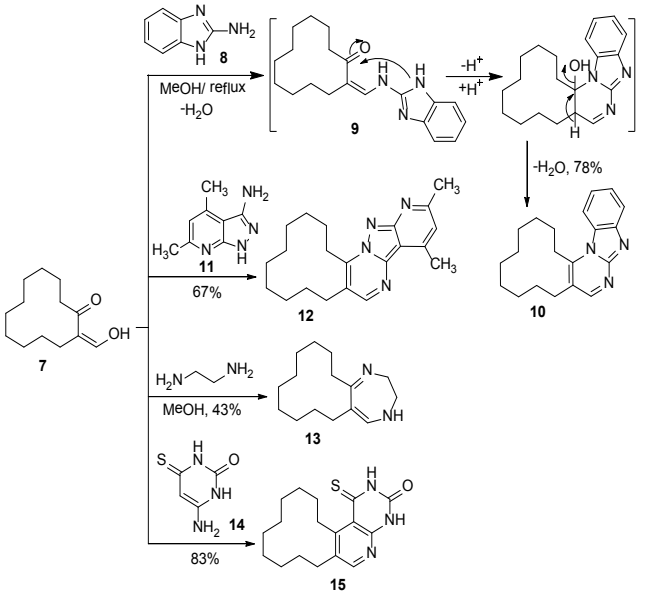
anticancer activity as well as inhibition of platelet aggregation and inhibition of steroid 5α-reductase. Coumarines are used in drug and pesticidal preparations; they have also found applications as photosensitizers, fluorescent and laser dyes[23,24]. Because of the significant activities of these molecules we have prepared the coumarin **5** through condensation of ethyl 2-oxocyclo-dodecane carboxylate (**1**) with *m*-cresol under Von Pechmann reaction conditions[25]. The chemical structure of **5** was proved by IR and mass spectra. Its IR spectrum displays a peak at υ 1706 cm^{-1} due to lactone carbonyl group. In addition, its mass spectrum was perfectly consistent with its chemical structure where it displays a molecular ion peaks at *m/z* 298 (20%).

Treatment of **1** with hydrazoic acid generated *in situ* from sodium azide and concentrated sulfuric acid in chloroform at low temperature furnished the azacyclotridecane derivative **6** in high yield. The IR spectrum of compound **6** showed a strong absorption at υ = 3316 cm^{-1} due to (NH) group. Also, the main characteristic features of the ^{1}H NMR spectrum of **6** was the presence of a signal at δ 6.2 (1H, singlet) which is assigned to the proton of (NH) group, the signal at δ 4.7 (1H) which is assigned to the proton on the carbon located between (NH) and ester groups and the multiplet signal at δ 4.2 ppm (2H) which is assigned to the methylene group next to the carbonyl group. The assignment of the NH group between the CO groups and the substituted carbon atoms in compound **6** is based on the previously reported studies by Hamama *et al*[26] and Schmidt *et al*[27].



Scheme 1. Synthesis of different heterocycles fused or including dodecamethylene ring

Synthetic methods available for the construction of rings fused to heterocyclic molecules are limited owing to vulnerability of hetero atoms to the well established conditions often employed in carbocyclic chemistry[28]. As a part of our studies on the reactivity and synthetic uses of 2- (hydroxymethylene)cyclododecanone (**7**), we now report an access for construction of 12-membered carbocyclic fused to heterocyclic ring systems under mild conditions. Thus, direct condensation of 2-(hydroxymethylene) cyclododecanone (**7**) with bifunctional nucleophiles proved to be an easy route for construction of fused heterocycles belonging to different classes. In this context benzimidazo [1,2-*a*]- 5,6,7,8,9,10,11, 12,13,14–decahydro[1]cyclododeca[d] pyri- midine (**10**) was synthesized by reaction of 2- (hydroxymethylene) cyclododecanone (**7**) with 2-amino- 1*H*- benzo [*d*]imidazole (**8**) in refluxing methanol whereby **10** was obtained in a good yield without isolation of the anticipated open intermediate **9** (Scheme 2). The IR spectrum of compound **10** revealed the tetracyclic structure due to the absence of any absorption at carbonyl group region. Moreover, the ^{1}H NMR spectrum of **10** indicated the presence of a singlet signal at δ 8.68 (1H) corresponding to the orphan proton of pyrimidine ring, two triplets at δ 2.8 and 2.9 each for (2H) assigned to the two methylenes next to the double bond, four characteristic signals at δ 7.36 (1H, t), 7.52 (1H, t), 7.93 (1H, d), 8.0 (1H, d) ppm, pointing out to the four protons of benzene ring besides the remaining aliphatic protons as three multiplet signals at δ 1.3-1.6 (12H), at 1.8 (2H) and at δ 2.0 (2H) ppm.



Scheme 2. Reaction of 2-(hydroxymethylene)cyclododecanone (**7**) with different primary amines

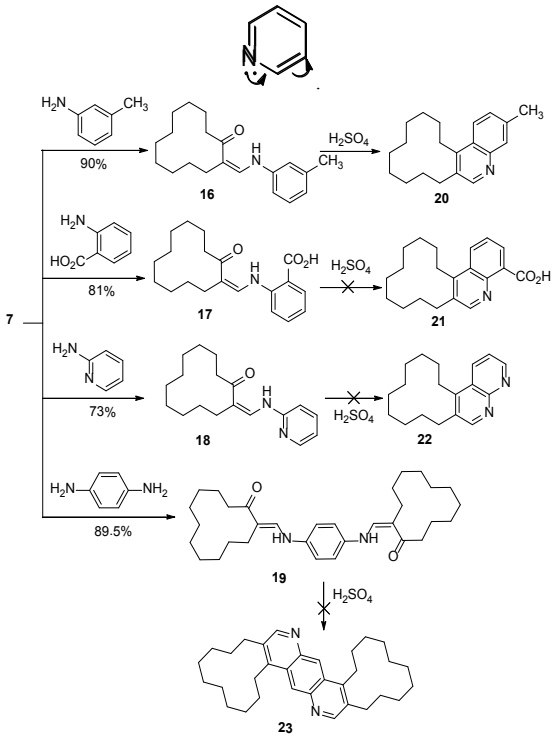
In addition, condensation of **7** with 3-amino-4,6- dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine (**11**) furnished directly the tetracyclicpyrazolo-pyrimidine **12** in very good yield. In the same context (1*Z*,5*Z*)-3,4,6,7,8,9,10,11,12,13,14, 15-dodecahydro-2*H*-[1]cyclododeca[*e*][1,4]diazepine (**13**) was synthesized by condensation of **7** with ethylene diamine. The mass spectrum of compound **13** displays molecular ion peaks at *m/z* 234 (M^+, 3.25).

Moreover, the pyridopyrimidine derivative **15** was prepared through condensation of **7** with 6-aminothio uracil **14**. The chemical structure of **15** was confirmed by IR and mass

spectra. Its mass spectrum was in great accordance with its chemical structure where it displays a molecular ion peaks at *m/z* 317 (32%, M^+).

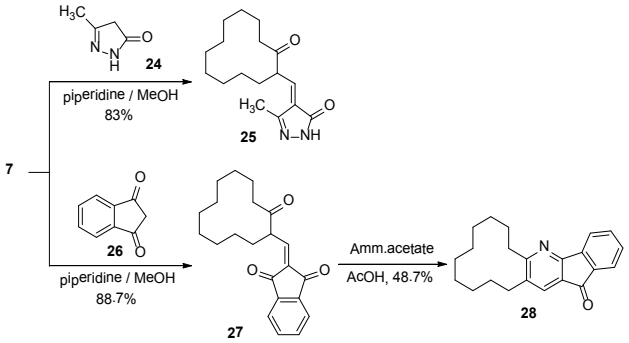
Enaminones are highly important versatile synthetic building blocks. They are key intermediates for compounds belonging to diverse heteocyclic classes. They are readily prepared by interaction of 1,3-dicarbonyl compounds and amines of different classes[29]. On this basis we prepared a series of enaminoketones to exploit them as intermediates for annulation of cyclododecane ring system with six-membered nitrogen containing heterocycles. Therefore, enaminones **16-19** were prepared by interaction of 2-(hydroxyl methylene)cyclododecanone (**7**) with the appropriate amines, namely; *m*-toluidine, anthranilic acid, 2-aminopyridine and *p*-pheneylenediamine, respectively (Scheme 3).

Spectral data of the newly prepared enaminoketones **16-19** are in accordance with their chemical structures. Furthermore, our trials to cyclize the enaminoketones **16-19** to their corresponding fused heterocycles **20-23** under the influence of concentrated sulfuric acid were unsuccessful, except, only the enaminoketone **16** was smoothly transformed to the quinoline derivative **20**. The explanation of these reactions in case of compound **21** the ortho position for cyclization is the meta position of the COOH group *i.e* deactivation for cyclization. Also, in case of compound **22** migration of lone pair of electrons for N atom as follow:



Scheme 3. Synthesis of enaminoketones **16-19** and trials to synthesize their fused heterocycles **20-23** under concentrated sulfuric acid influence

Moreover, the ortho position for cyclization is the meta position of the another NH group in case of compound **23**. Finally, we explored the base catalyzed condensation of 2-(hydroxymethylene)cyclododecanone (**7**) with active methylene compounds such as 3-methyl-1*H*-pyrazol-5(4*H*)-one (**24**) and 1,3-indanedione (**26**) to afford the corresponding alkylidenes **25** and **27**, respectively. The alkylidene **27** was easily transformed into the tetracyclic pyridine derivative **28** under the influence of ammonium acetate in glacial acetic acid (Scheme 4). The mass spectrum of **25** showed a molecular ion beak at m/z 290 (5%, M^+). Finally, the mass spectrum of alkylidene **27** and tetracyclic-pyridine derivative **28** showed the molecular ion peak at m/z 338 (8%, M^+) and 319 (33%, M^+), respectively. All compounds were confirmed by IR, ^{1}H NMR and mass spectra.



Scheme 4. Condensation of 2-(hydroxymethylene)cyclododecanone (**7**) with active methylene compounds

3. Conclusions

In this paper, compounds ethyl 2-oxocyclododecanecarboxylate (**1**) and 2-(hydroxymethylene)cyclododecanone (**7**) were used as starting compounds for the synthesis of the target compounds. Thus, compound **1** reacted with different nucleophiles at different reactions conditions to give pyrazolone **2**, isoxazolone **3** pyrimidinone **4**, coumarin **5** and azacyclotridecane **6** derivatives. Furthermore, compound **7** followed condensation reactions with bifunctional nucleophiles such as benzo[*d*]imidazole **8**, pyrazolo[3,4-*b*]pyridine **11**, ethylene diamine and 6-aminothiouracil **14** to give pyrimidine **10**, pyrazolopyrimidine **12**, diazepine **13** and pyridopyrimidine **15**, respectively. Moreover, enaminones **16-19** were obtained by interaction of **7** with the appropriate amines. Finally, the base catalyzed condensation of **7** with active methylene compounds afforded the corresponding alkylidenes **25** and **27**, respectively.

4. Experimental

All melting points are in degree centigrade (uncorrected) and were determined on Gallenkamp electric melting point apparatus. The IR spectra were recorded (KBr) on a Mattson 5000 FTIR spectrophotometer at Microanalytical Unit, Faculty of Science; Mansoura University. The ^{1}H NMR data were obtained in $CDCl_3$ or DMSO using TMS as internal standard and chemical shifts were reported in ppm (δ) downfield from internal TMS. The ^{1}H NMR spectra of compounds **2-4**, **6** and **10** were measured on a JEOL (500

MHz) spectrometer; Alexendria University. The mass spectra of compounds **5**, **6**, **12**, **15**, **20** and **28** were carried out on GCMS-QP 1000 EX Shimadzu Japan (Gas Chromatography-Mass spectrometer), National Research Center, Dokki, Giza, Egypt. The ^{13}C NMR spectrum for compound 17 (125 MHz) was performed on a Bruker Avance 500 spectrometer at Bioorganic Chemistry department, Saarland Saarbrüken University, Germany. The Mass spectra of compounds **2**, **10**, **13**, **16-19**, **25** and **27** were recorded on a Finnigan MAT 212 mass spectrometer instrument, Micro analytical unit Cairo University. Compounds **3** and **4** were recorded on 70 eV with a Varian MAT 311 instrument. Reactions were monitored by thin layer chromatography (TLC) using EM science silica gel coated plates with visualization by irradiation with ultraviolet lamp. The ethyl2-oxocyclododecanecarboxylate (**1**), and2-(hydroxymethylene)cyclododecanone (**7**) were prepared as previously cited in literature according to reported methods[30,31].

***N*-Phenyl-1,2,4,5,6,7,8,9,10,11,12,13-dodecahydro-cyclododecapyrazol-3-one (2)**. A mixture of **1** (1 g, 3.94 mmol) and phenyhydrazine (0.425 g, 0.387 mL, 3.94 mmol) was refluxed in acetic acid (20 mL, 50%) for 3 h, poured into ice-cold water while stirring, whereby a yellow precipitate was formed, filtered off and air dried, recrystallized from ethanol to furnish **2**. Yield 60%; mp 178-180°C; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 3277, 2931, 2858, 1697; ^1H NMR (500 MHz, DMSO) δ ppm: 1.1-1.5 (16 H, m), 1.75 (2H, t, *J*= 7.65 MHz), 2.05 (1H, m), 2.35 (1H, m), 2.65 (1H, m), 6.4 (1H, s), 7.15 (1H, t, *J*= 7.65 MHz), 7.4 (2H, t, *J* = 7.65 MHz), 7.75 (2H, d, *J*= 7.65 MHz); MS (EI, 70 ev): *m/z* (%): 298 (M^+, 7.24), 297 ($[M-H]^+$, 15), 77 (100); Anal. Calcd. for $C_{19}H_{26}N_2O$ (298.24): C, 76.47; H, 8.78; N, 9.39; Found: C, 76.66; H, 8.69; N, 9.32.

4,5,6,7,8,9,10,11,12,13-Decahydrocyclododeca[*c*]isoxazol-3(3a*H*)-one (**3**). A mixture of **1** (0.635 g, 2.5 mmol), hydroxylamine hydrochloride (0.174 g, 2.5 mmol) and pyridine (2 mL) was refluxed in methanol (10 mL) for 5 h, left to cool, poured into ice-cold water and acidified with conc. HCl whereby an oily product was formed. The oil was separated and triturated with petroleum ether to give a white precipitate. Recrystallization from a mixture of ethanol and DMF (10:1) afforded **3**. Yield 83%; mp 106-110°C; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 2930, 2853, 1673; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.1-1.7 (18H, m), 2.35 (2H, q, *J*= 6.90 MHz), 2.55 (1H, m); MS (EI, 70 ev): *m/z* (%): 223 (M^+, 24.3), 55 (100); Anal. Calcd. for $C_{13}H_{21}NO_2$ (223.19): C, 69.92; H, 9.48; N, 6.27; Found: C, 69.74; H, 9.75; N, 6.21.

2-Amino-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[*d*]pyrimidin-4(3*H*)-one (**4**). Guanidine nitrate (0.61 g, 5 mmol) was added to an ethanolic solution of sodium ethoxide[prepared by dissolving sodium (0.23 g, 10 mmol) in ethanol (30 mL)] then ketoester **1** (1.27 g, 5 mmol) was added. The reaction mixture was heated under reflux over steam bath for 8 h, left to cool whereby a white precipitate was formed and filtered off. Recrystallization from a mixture of ethanol and DMF (10:1) furnished compound **4**. Yield 80%; mp 260-262°C; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 2934, 2857, 3408, 3308, 3134, 2928, 2855; ^1H NMR (500 MHz, DMSO) δ ppm: 1.0-1.6 (16H, m), 2.25 (4H, t, *J*= 6.10 MHz), 6.5 (2H, s), 8.08 (1H, s); MS (EI, 70 ev): *m/z* (%): 249 (M^+, 20.9), 139 (100); Anal. Calcd. for $C_{14}H_{23}N_3O$ (249.22): C, 67.43; H, 9.30; N, 16.85 Found: C, 67.61; H, 9.22; N, 16.79.

3-Methyl-7,8,9,10,11,12,13,14,15,16-decahydro[1]cyclododeca[*c*]chromen-6-one (**5**). A mixture of the ketoester **1** (1.28 g, 5 mmol) and *m*-cresol (0.54 g, 5 mmol) was heated in sulfuric acid (10 mL, 75%) over steam bath for 1.5 h. Then, left to cool and poured into crushed ice whereby a white precipitate was formed, filtered off and dried in a dissicator (over anhydrous calcium chloride) then recrystallized from ethanol-water mixture (15: 2) to give **5**. Yield 68%; mp 75-77°C; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 2933, 2858, 1706; MS (EI, 70 ev): *m/z* (%): 298 (M^+, 20), 55 (100); Anal. Calcd. for $C_{20}H_{26}O_2$ (298.23): C, 80.50; H, 8.78; Found: C, 80.37; H, 8.82.

13-Oxo-azacyclotridecane-2-carboxylic acid ethyl ester (**6**). Ketoester **1** (1.28 g, 5 mmol) was added with stirring to a pre-cooled (salt-ice bath) mixture of (30 mL) chloroform and sulfuric acid (10 mL, 80%) then sodium azide (0.325 g, 5 mmol) was added portion wise over 1 h with stirring in salt-ice bath. The mixture was then heated over steam bath for 10 min; stirring was continued for additional 4 h at room temperature. The reaction mixture was then poured into ice-cold water and basified with concentrated ammonia solution whereby a gelatinous white precipitate was formed which then extracted with chloroform (3x20 mL). The combined chloroform extract was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford a white precipitate recrystallized from a mixture of methanol and DMF (10:1) to produce compound **6**. Yield 87%; mp 140-142°C; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 3316.9, 2921, 2858, 1741, 1708; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.29-1.30 (17H, m), 1.57 (2H, m), 2.07 (2H, m), 2.20 (2H, m), 4.2 (2H, m), 4.7 (1H, m), 7.25 (1H, s); MS (EI, 70 ev): *m/z* (%): 269 (M^+, 24), 196 (100); Anal. Calcd. for $C_{15}H_{27}NO_3$ (269.24): C, 66.88; H, 10.10; N, 5.20; Found: C, 66.77; H, 10.02; N, 5.17.

Benzimidazo[1,2-*a*]-5,6,7,8,9,10,11,12,13,14-decahydro[1]cyclododeca[*d*]pyrimidine (**10**). Compound **7** (0.53 g, 2.25 mmol) and 2-aminobenzimidazol (**8**) (0.3 g, 2.25 mmol) was completely dissolved in methanol (20 mL). The reaction mixture was refluxed for about 3 h after that it was left to cool overnight. Pale yellow crystals were separated, filtered off and air dried. Recrystallization from ethanol gave **10**. Yield 78%; mp 230°C; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 2921, 2860, 1633; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.3-1.6 (12H, m), 1.8 (2H, m), 2.0 (2H, m), 2.8 (2H, t, *J*= 7.60 MHz), 2.9 (2H, t, *J*= 7.65 MHz), 7.36 (1H, t, *J*= 7.60 MHz), 7.52 (1H, t, *J*= 7.65 MHz), 7.93 (1H, d, *J*= 8.40 MHz), 8.0 (1H, d, *J*= 8.40 MHz), 8.68 (1H, s); MS (EI, 70 ev): *m/z* (%): 307 (M^+, 100); Anal. Calcd. for $C_{20}H_{25}N_3$ (307.24): C, 78.14; H, 8.24; N, 13.67; Found: C, 77.93; H, 8.12; N, 13.58.

Synthesis of 13,15-dimethyl-1,2,3,4,5,6,7,8,9,10- decahydrocyclododeca[e]pyrido[2',3':3,4]pyrazolo[1,5-a] pyrimidine (12). A mixture of ketoaldehyde **7** (0.45 g, 2.1 mmol) and the pyrazolopyridine derivative **11** (0.35 g, 2.1

mmol) was dissolved in a mixture of MeOH (20 mL) and DMF (5 mL), The reaction mixture was then heated under reflux for 6 h, left to cool overnight, poured into crushed ice to afford a yellow precipitate which was collected by filtration under vacuum and air dried. Recrystallization from a mixture of ethanol and DMF (10:1) afforded **12**. Yield 67%; mp 130-133°C; 337 ($[M+H]^+$, 10.15), 336 (M^+, 26), 55 (100); Anal. Calcd. for $C_{21}H_{28}N_4$ (336.27): C, 74.96; H, 8.39; N, 16.65; Found: C, 74.85; H, 8.32; N, 16.61.

(1*Z*,5*Z*)-3,4,6,7,8,9,10,11,12,13,14,15-Dodecahydro-2*H*-[1]cyclododeca[*e*][1,4]diazepine (**13**). A mixture of ketoaldehyde **7** (0.53 g, 2.5 mmol) and ethylene-diamine (0.15 g, 0.17 mL, 2.5 mmol) was refluxed in methanol (20 mL) for 2.5 h, left to cool overnight, filtered off and air dried. Recrystallization from ethanol afforded diazepine **13**. Yield 43%; mp 260-264℃; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 3300, 2931, 2858, 1643; MS (EI, 70 ev): *m/z* (%):234 (M^+, 3.25), 235[$(M+H)^+$, 14.9], 222 (100); Anal. Calcd. for $C_{15}H_{26}N_2$ (234.24): C, 76.87; H, 11.18; N, 11.95; Found: C, 76.78; H, 11.15 N, 11.89.

Synthesis of 1-thioxo-1,2,7,8,9,10,11,12,13,14,15,16-dodecahydrocyclododeca[4,5]pyrido[2,3-*d*]pyrimidin-3(4*H*)-one (**15**). A mixture of ketoaldehyde **7** (0.53 g, 2.5 mmol) and 6-aminothiouracil (**14**) (0.36 g, 2.5 mmol) was refluxed in DMF (15 mL) for 4.5 h, then poured into crushed ice whereby a yellow precipitate was formed, filtered off and air dried then recrystallized from a mixture of ethanol and DMF (10:1) to afford **15**. Yield 83%; mp 148-150℃; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 3426, 3322, 2925, 2858, 1625; MS (EI, 70 ev): *m/z* (%): 317 (M^+, 32), 98 (100); Anal. Calcd. for $C_{17}H_{23}N_3OS$ (317.28): C, 64.32; H, 7.30; N, 13.24; Found: C, 64.21; H, 7.24; N, 13.18.

2[*N*-(*m*-Toluidino)methylene]cyclododecanone (16). Ketoaldehyde **7** (1.05 g, 5 mmol) was added to *m*-toluidine (0.54 g, 5 mmol) in methanol (20 mL). The reaction mixture was refluxed for 2 h, left to cool whereby a yellow precipitate was formed, filtered off and air dried then recrystallized from ethanol to give **16**. Yield 90%; mp 185-187℃; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 3253, 2926, 2853, 1636; MS (EI, 70 ev): *m/z* (%): 297 (M^+-2, 57), 298 (M^+-1, 12), 187 (100); Anal. Calcd. for $C_{20}H_{29}NO$ (299.26): C, 80.22; H, 9.76; N, 4.68; Found: C, 80.01; H, 9.59; N, 4.57.

2-[(2-Oxocyclododecylidene)methylamino]benzoic acid (17). Ketoaldehyde **7** (1.05 g, 5.0 mmol) was refluxed with a methanolic solution (25 mL) of anthranilic acid (0.68 g, 5.0 mmol) for 1 h. The reaction mixture was left to cool, filtered off and air dried. Recrystallization from ethanol furnished **17**. Yield 81%; mp 215-217℃; ^{1}H NMR (500 MHz, DMSO) δ ppm: 1.0-1.65 (16H, m), 2.35 (2H, m), 2.7 (2H, m), 4.04 (1H, s), 6.95 (1H, d, *J*= 7.65 MHz), 7.25 (1H, s), 7.65 (1H, t, *J*= 7.65 MHz), 7.9 (1H, t, *J*= 7.65 MHz), 8.05 (1H, d, *J*= 7.65 MHz), 10.7 (1H, s); ^{13}C NMR (125 MHz, DMSO): δ ppm: 20.97, 22.42, 22.51, 22.87, 23.70, 23.97, 24.80, 25.18, 25.52, 28.71, 117.01, 125.03, 127.69, 128.15, 134.16, 135.70, 138.35, 155.08, 178.42, 179.96; ^{13}C NMR (DEPT 135, T= 60℃, DMSO): indicates a presence of ten CH_2 and one CH groups; MS (70 eV): *m/z* = 329 (M^+, 49), 137 (100); Anal. Calcd. for $C_{20}H_{27}NO_3$ (329.24): C, 72.92; H, 8.26; N, 4.25; Found: C, 72.85; H, 8.22; N, 4.21.

2-[(Pyridin-2-ylamino)methylene]cyclododecanone (**18**). Ketoaldehyde **7** (1.05 g, 5 mmol) was added to 2-aminopyridin (0.47 g, 5.0 mmol) in methanol (20 mL) and allowed to react for about 3 h. The reaction mixture was left to cool over night whereby a crystalline white precipitate was formed, filtered off and air dried. Recrystallization from ethanol produced **18**. Yield 73%; mp 180-182℃; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 3319, 2926, 2856, 1654; ^{1}H NMR (500 MHz, DMSO) δ ppm: 1.0-1.65 (16H, m), 2.35 (2H, m), 2.7 (2H, m), 4.04 (1H, s), 6.95 (1H, t, *J*= 6.10 MHz), 7.25 (1H, s), 7.65 (1H, d, *J*= 7.65 MHz), 7.9 (1H, t, *J*= 6.10 MHz), 8.05 (1H, d, *J*= 8.03 MHz); MS (EI, 70 ev): *m/z* (%): 286 (M^+, 45), 145 (100); Anal. Calcd. for $C_{18}H_{26}N_2O$ (286.24): C, 75.48; H, 9.15; N, 9.78; Found: C, 75.39; H, 9.07; N, 9.71.

***Bis*-2-[*N,N'*-(*p*-phenylenediaminomethylene)]cyclododecanone** (**19**). Ketoaldehyde **7** (0.53 g, 2.5 mmol) was mixed with *p*-phenylenediamine (0.14 g, 1.25 mmol) in methanol (20 mL). The reaction mixture was refluxed for 1 h then poured into ice cold water. A greenish precipitate was formed, filtered under suction and air dried. Recrystallization from ethanol gave **19**. Yield 89.5%; mp 110℃; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 3340, 2929, 2856, 1635; MS (EI, 70 ev): *m/z* (%): 492 (M^+, 100); Anal. Calcd. for $C_{32}H_{48}N_2O_2$ (492.43): C, 78.00; H, 9.82; N, 5.69; Found: C, 78.11; H, 9.77; N, 5.64.

3-Methyl-7,8,9,10,11,12,13,14,15,16-decahydro-[1]cyclododeca[*c*]quinoline (**20**). A mixture of enaminoketone **16** (0.3 g, 1 mmol) and concentrated sulfuric acid (5 mL) was heated over a steam bath for 3 h. Poured into crushed ice then basified with ammonium hydroxide whereby a white precipitate was formed, filtered off and recrystallized from methanol to give **20**. Yield 53%; mp 108-110℃; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 2923, 2877, 1633; MS (EI, 70 ev): *m/z* (%): 281 (M^+, 18), 98 (100); Anal. Calcd. for $C_{20}H_{27}N$ (281.24): C, 85.35; H, 9.67; N, 4.98; Found: C, 85.27; H, 9.63; N, 4. 92.

3-Methyl-4-((2-oxocyclododecyl)methylene)-1*H*-pyrazol-5(4*H*)-one (**25**). To a mixture of ketoaldehyde **7** (1.05 g, 5.0 mmol) and pyrazolone **24** (0.73 g, 5 mmol) in methanol (20 mL) a few drops of piperidine were added. The reaction mixture was heated under reflux for 2 h. Removal of solvent under vacuum affording a reddish precipitate which upon recrystallization from methanol afforded **25**. Red crystals; yield 83%; mp 231-234℃; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 3212, 2920, 2859, 1706, 1592; MS (EI, 70 ev): *m/z* (%): 290 (M^+, 5.77), 206 (100); Anal. Calcd. for $C_{17}H_{26}N_2O_2$ (290.24): C, 70.31; H, 9.02; N, 9.65; Found: C, 70.22; H, 9.00; N, 9.61.

2-((2-Oxocyclododecyl)methylene)-2*H*-indene-1,3-dione (**27**). To a mixture of ketoaldehyde **7** (1.05 g, 5 mmol) and 1,3-indandione (**26**) (0.73 g, 5 mmol) in methanol (20 mL), a few drops of piperidine were added. The reaction mixture was heated under reflux for 3 h, poured into crushed ice and acidified with HCl. A brown precipitate was formed, filtered off, air dried and recrystallized from ethanol to give **27**. Yield 88.7%; mp 120-124℃; IR (KBr) $\acute{\upsilon}_{max.}$ cm^{-1}: 2929, 2858, 1708, 1629; MS (EI, 70 ev): *m/z* (%): 338 (M^+, 7.26), 55 (100); Anal. Calcd. for $C_{22}H_{26}O_3$ (338.23): C, 78.07; H, 7.74;

Found: C, 78.00; H, 7.70.

Indenopyridine derivative (**28**). Alkylidine **27** (0.6 g, 1.8 mmol) was dissolved in glacial acetic acid (15 mL) containing (2 g) ammonium acetate, the reaction mixture was then heated under reflux for 5 h. Left to cool, then poured into crushed ice whereby, a grey precipitate was formed, filtered off, dried and recrystalized from a mixture of ethanol and DMF (10:1) to afford **28**. Yield 48.7%; mp 134-136°C; IR (KBr) $\upsilon_{max.}$ cm^{-1}: 2925, 2854, 1708; MS (EI, 70 ev): *m/z* (%): 319 (M^+, 35), 320[$(M+H)^+$, 28], 209 (100); Anal. Calcd. for $C_{22}H_{25}NO$ (319.23): C, 82.72; H, 7.89; N, 4.38; Found: C, 82.66; H, 7.83; N, 4.32.

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