Chapter 3
Section A

Synthesis towards 7,8-substituted coumarin
Introduction

Coumarin 1 (benzo-α-pyrone) and flavonoid 2 (benzo-γ-pyrone) are members of benzopyrone systems, which are found in many vegetables, seeds, fruits like bilberry, nuts, coffee, tea, cinnamon bark oil and wine. Synthetic coumarins are widely used as aroma chemicals because of their odour strength, stability to alkali and relatively cheap price. Applications of coumarins include use as a sweetener and fixative (in perfumes), fragrance enhancers (for natural essential oils), blenders (in soaps and detergents), aroma enhancers (in tobacco) and for imparting pleasant odours to industrial products. Variety of flavonoids show in vitro antibacterial, antifungal and antiviral activities. The flavonol glycosides were used for the treatment of cold, fever, headache, cough, and faucitis.

![Figure 1](image1.png)

The IUPAC nomenclature for coumarin is 2H-1-benzopyran-2-one. Coumarins are classified in four main classes, namely simple coumarins like compound 3, furanocoumarins as linear compound 4 or angular compound 5, pyranocoumarins like 6 and 7 and pyrone-substituted coumarins like 8 as shown in Figure 2.

![Figure 2](image2.png)

The 7, 8-disubstituted coumarins are also found abundantly in nature. Some of them are shown in Figure 3.
Figure 3

The 7, 8-sunstituted coumarin 13 was isolated from the leaves of *Galipea panamensis*. It was tested against axenic amastigote forms of *Leishmania panamensis* and displayed EC$_{50}$ of 10.5 µg/mL. It also displayed cytotoxicity (IC$_{50}$) at concentrations of 33.0 µg/mL on human promonocytic U-937 cells.

There is only one synthetic report for the compound 13 as shown below.


Present Plan

Considering the biological importance and only one synthetic report for coumarin 13, a new strategy was envisioned for its synthesis which involves construction of furan ring at the end. The retrosynthetic plan is shown in Scheme 1.
In the present synthetic plan, Heck reaction\(^7\) is a key step. In the Heck reaction, a vinyl or aryl halide (or triflate) reacts with an alkene in the presence of a base and a palladium catalyst to produce a new alkene. The mechanism follows a Pd(0)/Pd(II) catalytic cycle. The substitution reactions on planar sp\(^2\) hybridized carbon center are possible by Heck reaction and hence it is one of the important reactions for the C-C bond formation. This palladium catalyzed Heck reaction is the most extensively used reaction for the synthetic purpose. The representative Heck reaction is shown in Figure 4. There is a possibility of getting two regioisomers as A and B.

![Scheme 1. The retrosynthetic plan](image)

The Heck reaction between alkene and halide is accomplished by the use of an organopalladium catalyst, a ligand, and a base.

The reagent details of Heck reaction are mentioned below.

The halides can be Br, Cl, I or triflate with R\(^1\) group as aryl or vinyl. The order of reactivity of aryl halides and triflates (I > OTf > Br >> Cl) is according to the bond strength of the C–X bond. Alkene should have at least one hydrogen and preferably
an electron withdrawing group such as acrylate ester or acrylonitrile. The catalysts for the reaction are tetrakis(triphenylphosphine)palladium, Pd(PPh$_3$)$_4$; palladium acetate, Pd(OAc)$_2$; palladium chloride, (PdCl$_2$); tris(dibenzylideneacetone)dipalladium(0), Pd$_2$(dba)$_3$ etc. The commonly used ligands are triphenylphosphine, (PPh$_3$); PHOX, or BINAP and the bases are Et$_3$N, K$_2$CO$_3$, Ag$_2$CO$_3$, NaOAc etc. The reaction is carried out in solvents such as toluene, THF or DMF.

The mechanism of Heck reaction is shown$^7$ in Figure 5. The palladium(0) required for this cycle is generally prepared in situ from a palladium(II) source. For example palladium(II) acetate is converted to bis(triphenylphosphine)palladium(0) using triphenylphosphine as a reductant which is oxidized to triphenylphosphine oxide in situ. First step is an oxidative addition in which palladium inserts itself in the aryl-halide bond. Then palladium forms a π complex with the alkene and in the next step the alkene inserts itself in the palladium carbon bond in a syn fashion. Then trans isomer was formed by rotation to relieve a torsional strain (not shown) and then, a β-hydride elimination gave product alkene with the formation of a new palladium alkene π complex. This complex is destroyed in the next step where palladium(0) compound is regenerated from palladium(II) by reductive elimination with the base.

![Figure 5. Mechanism of Heck reaction](image-url)
Various halides like aromatic, heterocyclic halides are used in the Heck reaction. Some examples of Heck reaction are shown below.


3. Arasambattu K. et al (1996)\(^10\)

5. Sukla, N. et al (2012)\textsuperscript{12}

The literature showed very few reports of Heck reaction using halocoumarins instead of aromatic halides as shown below.

1) Gillmore, A. (2003)\textsuperscript{13}

2) Bariamis, S. E. (2013)\textsuperscript{14}
Results and Discussion

According to the plan, the synthetic target was coumarin 13. The synthesis started with the Pechmann reaction of resorcinol 14 with malic acid 15 in conc. H₂SO₄ which gave umbelliferone 3 as a solid having m.p. 233 °C (Scheme 2). ¹H NMR (Figure 10) of 3 showed four doubles and a doublet of doublet. The assignment of signals was carried out from the observed coupling constants. The cis coupling constants of 9.46 and 9.16 Hz of the signals at δ 6.20-6.22 and δ 7.93-7.95 indicated that these two are due to C₃H and C₄H. The doublet of one proton at δ 6.71-6.72 with J = 2.44 Hz was due to C₈H (meta coupling) and the doublet for one proton at δ 7.52-7.54 with J = 8.54 Hz, was due to C₅H (ortho coupling). The doublet of doublet for one proton at δ 6.78-6.80 with J = 8.39, 2.29 Hz, was due to C₆H (ortho and meta coupling) and the singlet for one proton at δ 10.57 was for phenolic hydroxyl group. ¹³C NMR (Figure 11) showed nine singlets in aromatic region from 102.63 to 161.76. The NMR values were in good agreement with the reported data.

Umbelliferone 3 was iodinated using reported procedure where I₂ in aqueous KI was used to give 8-iodo umbelliferone 16. Due to very poor solubility, NMR of this compound was taken in deuterated methanol. ¹H NMR (Figure 12) showed four doublets at δ 6.10-6.12, 6.75-6.77, 7.33-7.35, 7.68-7.70 with J = 9.46, 8.55, 8.55, 9.16 Hz respectively. ¹³C NMR (Figure 13) showed nine singlets at appropriate positions including an expected upfield singlet at δ 74.39 for the carbon adjacent to iodine. The NMR values were consistent with the reported data.

Further, methoxylolation of compound 16 was carried out using methyl iodide, and K₂CO₃ in dry acetone which gave 8-ido-7-methoxy coumarin 17 in 82% yield. It exhibited singlet at δ 4.0 in ¹H NMR (Figure 14) and at δ 50 in ¹³C NMR spectrum (Figure 15) for methoxy group and other signals at their appropriate positions. All this data was consistent with the reported values.
The diester 19 was obtained\(^{17}\) from citraconic anhydride 18 by treating it with methanol/H\(_2\)SO\(_4\) (Scheme 3). The \(^1\)H NMR (Figure 16) showed multiplet at \(\delta 1.97\) - 2.07 for protons of methyl group on the double bond, multiplets at \(\delta 3.67\) - 3.72 and 3.77 - 3.82 for six protons of two methyls of ester groups and multiplet at \(\delta 5.81\) - 5.86 for one olefinic proton. \(^{13}\)C NMR (Figure 17) showed singlet for carbon of the methyl group on double bond at \(\delta 20.35\), two singlets for two methyl carbons of esters at \(\delta 51.70, 52.24\), singlets at \(\delta 120.49, 145.61\) for olefinic carbons and singlets at \(\delta 165.24, 169.24\) for two carbonyl carbons.

The Heck reaction of iodocoumarin 17 with olefin 19 was carried out using (o-tolyl)\(_3\)P, triethyl amine, and Pd(OAc)\(_2\) in DMF. After the usual workup and column chromatographic separation, two products were obtained in 91\% yield. Major product was in 91\% and minor was in 9\% yield. HRMS of the major product showed m/z value of 355.0793 corresponding to the mass of C\(_{17}\)H\(_{16}\)NaO\(_7\) (M+Na\(^+\)). Both the compounds were characterized by NMR technique. \(^1\)H NMR (Figure 18) of major product displayed a singlet at \(\delta 3.29\) for two protons, a singlet at \(\delta 3.69\) for three protons, two singlets at \(\delta 3.86\) and 3.87 for three protons each, singlet at \(\delta 7.70\) for one olefinic proton, four doublets for four aromatic protons at \(\delta 6.28\) and 7.65 with \(J = 9.46\) Hz and at \(\delta 6.90\) and 7.47 with \(J = 8.85\) Hz. \(^{13}\)C NMR (Figure 19) exhibited four singlets at \(\delta 34.97, 51.99, 52.34, 56.13\) for aliphatic carbons and remaining
thirteen singlets for aromatic carbons. This NMR data was compared with the expected structure 20. However, singlet for protons of methyl group on double bond was absent and a methylene group was observed at δ 3.29 for two protons. In addition to this, one olefinic proton was also seen as a singlet at δ 7.70. Thus, from all the above spectral data, structure 21 was assigned to the major product. The minor product showed a singlet at δ 3.89 for methoxy group and five aromatic protons between δ 6.27 to 7.66 in 1H NMR spectrum (Figure 20). 13C NMR (Figure 21) displayed singlet at δ 55.79 for methoxy group and singlets for other aromatic carbons. From this data, the minor product was shown to be the de-iodinated18 compound 22. Thus, in the Heck coupling reaction, the expected product 20 was not obtained and an unreported compound 21 was resulted as a major product along with compound 22 as a minor product.

According to the mechanism, two pathways are envisioned for this conversion as shown below (Figure 6). During the coordination of olefin to palladium, due to the hyperconjugation effect of methyl protons, the coordination of double bond takes place19 at two positions. The intermediates C’ and D’ are supposed to give products C and D respectively. Now in case of 8-iodo-7-methoxycoumarin, due to steric demand of the two ortho substituents, (E and F in Figure 6), it disfavors β-hydride elimination in E producing 20. Hence only product 21 is formed over 20. A competitive
dehalogenation process led to dehalogenated product 22 in minor amount along with product 21.

Figure 6
Thus, we could not get the required product 20, which was the precursor for the furan ring. The further modification in the Heck reaction using other reaction conditions is in progress.

Subsequently, another route was envisioned for the synthesis of the target molecule 13. The retrosynthesis was planned as shown below.

![Scheme 5. The retrosynthetic plan](image)

This route involves use of Sonogashira coupling reaction. The Sonogashira coupling reaction is a cross-coupling reaction between a terminal alkyne and an aryl or vinyl halide to form carbon–carbon bond using palladium catalyst, Cu(I) salt and base. The representative example is shown below.

![Figure 7. The representative Sonogashira coupling reaction](image)

Commonly used palladium catalysts are Pd(PPh₃)₄, Pd(PPh₃)Cl₂, bidentate ligand catalysts, such as Pd(dppe)Cl, Pd(dppp)Cl₂, and Pd(dppf)Cl₂. Cu(I)X is used as a co-catalyst to increase the rate of the reaction. Triethylamine, diethylamine, potassium carbonate or cesium carbonate are used as bases.

The mechanistic path is shown in Figure 8. The palladium cycle is similar to the Heck reaction i.e. oxidative addition, transmetallation, and reductive elimination. Copper cycle is also involved in the same mechanism. In the presence of base, the formation of a pi-alkyne complex, makes the terminal proton on the alkyne more acidic. This leads to the formation of the copper acetylide B, which reacts with the palladium intermediate, with regeneration of the copper halide.
Figure 8. Mechanism of Sonogashira coupling reaction

Following are some examples illustrating the use of Sonogashira coupling reaction.

1. Miller, M. W. (1997)\textsuperscript{21}

\[
\text{I} + \text{R} \rightarrow \text{OH} \rightarrow (+)\text{-harveynone}
\]

2. Yamashita, M. (2011)\textsuperscript{22}

\[
\text{X} + \text{R}_2 \rightarrow \text{Indolequinones}
\]
Coming to the present work, Sonogashira coupling reaction of 8-iodo umbelliferone 17 with propargyl alcohol 23 using triethylamine, freshly prepared tetrakis(triphenylphosphine)palladium catalyst and copper (I) iodide in dry THF was carried out. It gave product 24 in 70% yield after chromatographic purification (Scheme 6). The $^1$H NMR (Figure 22) showed singlet for methoxy protons at $\delta$ 3.98. The alcoholic proton (OH) was coupling with protons of CH$_2$ group and hence OH resonance appeared as a triplet at $\delta$ 4.45 with $J$ =6.20 Hz. The mutually coupled methylene protons near the alcoholic group showed doublet at $\delta$ 4.58 with the same coupling constant. The remaining four aromatic protons were resonating at the appropriate positions. $^{13}$C NMR (Figure 23) showed singlets at $\delta$ 50.85 for methylene carbon, at $\delta$ 56.23 for methoxy group and at $\delta$ 73.78 and 99.28 for acetylenic carbons. The remaining nine carbons were resonating at the appropriate positions. Thus, coumarin substituted propargyl alcohol 24 was synthesized in this reaction.

Scheme 6. Sonogashira coupling reaction of 17 with propargyl alcohol

The substituted furan can be synthesized by using magnesium mediated carbometallation$^{24}$ of propargyl alcohol (Scheme 9). The mechanism involves the
direct addition of Grignard reagent to propargyl alcohol to generate the intermediate magnesium chelate C. Subsequently, reaction with dimethylformamide (DMF) would produce intermediate hemiacetal D and further acidification would give 3,4-disubstituted furan.

![Figure 9. Magnesium mediated carbometallation of propargyl alcohol](image)

By using same analogy, it was planned to synthesize furan ring with coumarin substitution at 3 position (Scheme 7). Thus, the Grignard reaction of CH₃MgCl with substituted propargyl alcohol 23, followed by addition of DMF and subsequently acidification by p-TSA was carried out. The reaction mixture was worked up by usual procedure to get a crude product. On TLC it showed a new spot long with the spot of the starting compound 23. As only two compounds were seen on the TLC plate, the HRMS of crude compound was taken. It showed a molecular ion peak at 279.0935 (M+Na; C₁₅H₁₂O₄Na) in HRMS for target molecule along with molecular ion peak at 253.0470 (M+Na; C₁₃H₁₀O₄Na) corresponding to the reactant 23.

![Scheme 7.](image)

Thus, the formation of the target molecule 13 was identified from the HRMS results. The attempts to standardize the above reaction for getting good yield and further characterization of the product 13, is in progress.
Conclusion

A synthetic plan envisioned for the target molecule 13 using Heck coupling reaction could not be completed since a new product was obtained in the Heck reaction. Subsequently, another route having magnesium mediated carbometallation reaction as a key step was attempted. The formation of targeted product 13 was confirmed by HRMS. The standardization and final confirmation of the structure of the product 7-Methoxy-8-(4-methyl-3-furyl)-2H-chromen-2-one (13) is in progress.
Experimental Section

7-Hydroxy coumarin (umbelliferon, 3)

A mixture of resorcinol (5.5 g, 50 mmol), malic acid (6.7 g, 50 mmol) and conc. H₂SO₄ (50 ml) was stirred for half an hour then heated at 90°C for 2 h. Cooled and ice was added, precipitate was obtained which was filtered washed with water. The product was recrystallized from ethanol to get light yellow coloured product in 81%. M.p. 233°C.

¹H NMR (500 MHz, DMSO-d₆): δ ppm 6.20-6.22 (d, J = 9.46 Hz, 1H) 6.71-6.72 (d, J = 2.44 Hz, 1H) 6.78-6.80 (dd, J = 8.39, 2.29 Hz, 1H) 7.52-7.54 (d, J = 8.54 Hz, 1H) 7.93-7.95 (d, J = 9.16 Hz, 1H) 10.57 (s, 1 H).

¹³C NMR (126 MHz, DMSO-d₆): δ ppm 74.39, 113.02, 113.91, 114.85, 130.59, 145.93, 156.79, 162.88, 163.23.

HRMS (ESI): m/z calcd for C₉H₇O₃(M+H)+, 163.0390; found, 163.0392.

7-Hydroxy-8-iodo-2H-chromen-2-one (16)

Umbelliferone (I) (200 mg, 1.23 mmol) was dissolved in a 20% NH₄OH solution (5 mL) to which a solution of I₂ (313 mg, 1.23 mmol) dissolved in aqueous KI (5%, 10 mL) was added dropwise. After 1.5 h, the reaction was quenched with 2.5 N H₂SO₄ until acidic and precipitation occurred. The solid was filtered and purified with silica gel column chromatography using 5:95 ethyl acetate: DCM to afford the desired product as a yellow solid (318 mg, 90%). M.p. 224°C.

¹H NMR (500 MHz, CD₃OD): δ 6.10-6.12 (d, J = 9.46 Hz, 1H) 6.75-6.77 (d, J = 8.55 Hz, 1H) 7.33-7.35 (d, J = 8.55 Hz, 1H) 7.68-7.70 (d, J = 9.16 Hz, 1H)

¹³C NMR (126 MHz, CD₃OD): δ 74.39, 113.02, 113.91, 114.85, 130.59, 145.93, 156.79, 162.88, 163.23.

HRMS (ESI): m/z calcd for C₉H₆IO₃(M+H)+, 288.9356; found, 288.9347.
8-Iodo-7-methoxycoumarin (17)

A mixture of 8-iodoumbelliferone (600 mg, 2.08 mmol), methyl iodide (0.25 ml, 4.1 mmol, 2.0 equiv.) and anhydrous potassium carbonate (574 mg, 4.1 mmol, 2.0 equiv.) in anhydrous acetone (20 ml) was heated to reflux for 5 h. Dilute aqueous hydrochloric acid solution (5 ml) followed by water (20 ml) were added. The mixture was extracted with dichloromethane (3x20 ml), and the combined organic extracts were washed with brine (60 ml), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO₂: EtOAc/n-hexane, 1:3) to give the title compound as pale cream coloured needles (520 mg, 82%). M.p. 160°C.

1H NMR (300 MHz, CDCl₃): δ 4.00 (s, 3H), 6.26-6.29 (d, J = 9.54 Hz, 1H), 6.80-6.83 (d, J = 8.58 Hz, 1H), 7.43-7.46 (d, J = 8.58 Hz, 1H), 7.57-7.60 (d, J = 9.54 Hz, 1H).

13C NMR (75 MHz, CDCl₃): δ 56.99, 76.04, 107.37, 113.72, 113.92, 129.03, 143.02, 155.03, 160.47, 161.67.

HRMS (ESI): m/z calcd for C₁₀H₈IO₃ (M+H)+, 302.9513; found, 302.9514.

Dimethyl methylmalolate (19)

To a solution of citraconic anhydride (4.48 g, 40 mmol) in methanol (40 mL) was added H₂SO₄ (4 mL) and mixture was refluxed for 12 h under nitrogen atmosphere. The reaction mixture was concentrated using rotary evaporator under vacuum. The residue was diluted with water and extracted with ethyl acetate (20 mL X 3). The combined organic layer was washed with aqueous solution of NaHCO₃, brine, and dried over Na₂SO₄. Concentration of organic layer in vacuo gave pure diester 8 as thick oil in 75%.

1H NMR (500 MHz, CDCl₃): δ 2.00-2.06 (m, 3H), 3.66-3.72 (m, 3H), 3.77-3.82 (m, 3H), 5.77-5.88 (m, 1H).

13C NMR (125 MHz, CDCl₃): δ 20.34, 20.35, 51.68, 51.70, 52.24, 52.26, 120.49, 145.61, 165.24, 169.24.
Dimethyl 2-((7-methoxy-2-oxo-2H-chromen-8-yl)methyl)maleate (21)

A mixture of iodide 17 (0.2 g, 0.66 mmol), dimethyl methylmaleate 19 (0.52 g, 3.28 mmol), (o-tolyl)₃P (0.1 g, 0.32 mmol) and triethyl amine (1.0 mL, 7 mmol) in DMF (10 mL) was degassed at 0 °C. Then, Pd(AcO)₂ (0.025 g, 0.11 mmol) was added and the resulting mixture was redegassed at the same temperature. The resulting reaction mixture was heated at 90 °C with vigorously stirring. The reaction was monitored by TLC. After the total consumption of the starting material, the mixture was passed through a short celite pad. The precipitate on the filter was washed with a small volume of DMF and the filtrates were combined and diluted with CHCl₃. The organic phase was washed with H₂O, dried over Na₂SO₄ and separated by column chromatography using silica gel using pet ether-ethyl acetate as eluent to give product 21 as a brownish solid having M. p. 79 °C (91%) along with 22 as a brownish solid having M. p. 82 °C (9%).

¹H NMR (500 MHz, CDCl₃): δ 3.29 (s, 2H), 3.69 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 6.27-6.29 (d, J = 9.46 Hz, 2H), 6.89-6.91 (d, J = 8.85 Hz, 2H), 7.46-7.48 (d, J = 8.85 Hz, 2H), 7.64-7.66 (d, J = 9.46 Hz, 2H), 7.70 (s, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 34.97, 51.99, 52.34, 56.13, 107.53, 112.03, 112.92, 113.69, 129.36, 130.64, 131.03, 143.35, 152.42, 159.53, 160.25, 167.13, 171.12.

HRMS (ESI): m/z calcd for C₁₇H₁₆O₇(M+Na)⁺, 355.0788; found, 355.0793.

7-methoxy-2H-chromen-2-one (22)

¹H NMR (500 MHz, CDCl₃): δ 3.89 (s, 3H), 6.26-6.28 (d, J = 9.77 Hz, 1H), 6.83-6.84 (d, J = 2.44 Hz, 1H), 6.85-6.88 (m, 1H), 7.38-7.40 (d, J = 8.54 Hz, 1H), 7.65-7.67 (d, J = 9.77 Hz, 1H).

DEPT (125 MHz, CDCl₃): δ 55.79, 100.86, 112.61, 113.12, 128.76, 143.42.
Preparation of tetrakis(triphenylphosphine)palladium

Palladium chloride (0.1 g) and triphenyl phosphine (0.74 g) were added to dimethyl formamide (7.5 mL) heated to 140 °C and stirred at this temperature for 1 h. Then reaction mixture was then cooled to 80 °C over a period of 1 h and a 25% aq. hydrazine solution (0.55 mL) was dropped cautiously of generation of nitrogen gas. After the mixture was stirred at 80-85 °C for 30 min, it was cooled to rt. Green crystals obtained, were collected by filtration under a nitrogen stream. The crystals were washed with ethanol and then with hexane. The crystals were dried under reduced pressure which gave deep green crystalline tetrakis(triphenylphosphine)palladium (0.6 g) 95% which is used immediately for next reaction. M.p. 128 °C.

8-(3-hydroxyprop-1-yn-1-yl)-7-methoxy-2H-chromen-2-one (24)

To a stirred solution of the iodide 17 (0.5 g, 1.65 mmol) in degassed tetrahydrofuran (20 ml) was added triethylamine (4.8 mL, 3 ml per mmol). The tetrakis(triphenylphosphine)palladium (0.38 g, 20 mol%) was added further propargyl alcohol (0.14 mL, 0.13 g, 2.48 mmol) was added. The mixture was refluxed under nitrogen for 1 h. Then copper (I) iodide (0.06 g, 20 mol%) was added. Refluxing was continued for 18 h, then the mixture was cooled to room temperature and treated with water (10 ml). Stirring was continued for 4 h then the mixture was separated and the aqueous layer was extracted with ether (3 × 15 mL). The combined organic solutions were washed with water (15 mL) and brine (15 ml) then dried over Na₂SO₄ and concentrated. The desired product was purified by column chromatography to get pale yellow solid compound in 70%. M. p. 105 °C.

1H NMR (300 MHz, CDCl₃): δ 3.98 (s, 3H), 4.45 (t, J = 6.20 Hz, 1H), 4.57-4.59 (d, J = 6.20 Hz, 2H), 6.26-6.29 (d, J = 9.54 Hz, 1H), 6.87-6.90 (d, J = 9.06 Hz, 1H), 7.42-7.45 (d, J = 8.58 Hz, 1 H), 7.65-7.68 (d, J = 9.54 Hz, 1 H).

13C NMR (75 MHz, CDCl₃): δ 50.85, 56.23, 73.78, 99.28, 100.91, 107.06, 112.50, 113.23, 128.31, 143.11, 155.26, 160.19, 162.89.

HRMS (ESI): m/z calcd for C₁₃H₁₀NaO₄ (M+H)+, 253.0471; found, 253.0475.
7-Methoxy-8-(4-methyl-3-furyl)-2\textit{H}-chromen-2-one (13)

Methylmagnesium chloride (1.39 mL, 1.87 M in THF, 1.39 mmol) was added to a solution of propyn-1-ol (24, 0.1 g, 0.43 mmol) in cyclohexane (4.1 mL) at 22°C. The solution was refluxed for 19 h. The solution was cooled to 0 °C and dimethylformamide (0.107 mL, 1.38 mmol) was added. The mixture was stirred for 5 min at 0 °C and refluxed for 3 h. Standard workup yielded the crude lactol which was immediately dissolved in benzene and treated with a catalytic amount of \textit{p}-toluenesulfonic acid and stirred at 22 °C for 2 h. The reaction was neutralized with saturated aqueous sodium bicarbonate, extracted with ether (3x10 mL), dried, concentrated. The HRMS of crude mass was taken.

HRMS (ESI): m/z calcd for 279.0633 (M+Na; C\textsubscript{15}H\textsubscript{12}O\textsubscript{4}+Na) Found 279.0935.
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$^1$H and $^{13}$C NMR spectra of products

**Figure 10.** $^1$H-NMR spectrum of 3 (500MHz, DMSO-$d_6$)

**Figure 11.** $^{13}$C-NMR spectrum of 3 (125MHz, DMSO-$d_6$)
Figure 12. $^1$H-NMR spectrum of 16 (500MHz, Methano-d$_4$)

Figure 13. $^{13}$C-NMR spectrum of 16 (125MHz, Methano-d$_4$)
Figure 14. $^1$H-NMR spectrum of 17 (500MHz, CDCl$_3$)

Figure 15. $^{13}$C-NMR spectrum of 17 (125MHz, CDCl$_3$)
Figure 16. $^1$H-NMR spectrum of 19 (500MHz, CDCl$_3$)

Figure 17. $^{13}$C-NMR spectrum of 19 (125MHz, CDCl$_3$)
Figure 18. $^1$H-NMR spectrum of 21 (500MHz, CDCl$_3$)

![H-NMR spectrum of 21](UMB_5_H.ESP)

Figure 19. $^{13}$C-NMR spectrum of 21 (125MHz, CDCl$_3$)

![C-NMR spectrum of 21](UMB_5_13C.ESP)
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**Figure 20.** $^1$H-NMR spectrum of 22 (500MHz, DMSO-$d_6$)

**Figure 21.** DEPT spectrum of 22 (125MHz, DMSO-$d_6$)
**Figure 22.** $^1$H-NMR spectrum of 24 (500MHz, CDCl$_3$+DMSO-$d_6$)

**Figure 23.** $^{13}$C-NMR spectrum of 24 (500MHz, CDCl$_3$+DMSO-$d_6$)
References


Section B

Attempt towards biologically active Bis-Indole Alkaloid, Hyrtinadine A
Introduction

Bis-indole alkaloids are the alkaloids having two indole moieties. Over a past few decades, a number of bis-indole metabolites containing either an imidazole or piperazine derivative have been isolated. The bis-indole alkaloids, nortopsentins A-D (Figure 1, 1-4) displayed\textsuperscript{1-4} cytotoxic activity against P-388 cells with IC\textsubscript{50} values of 7.6, 7.8, 1.7 and 0.9 μg/mL respectively. The bisindole alkaloid, topsentin (5) inhibited\textsuperscript{5} the proliferation of cultured human and murine tumor cells. It exhibited in vitro activity against P-388 with IC\textsubscript{50} 3 μg/mL and human tumor cell with IC\textsubscript{50} 20 μg/mL. Deoxytopsentin (6) showed\textsuperscript{6} the antiproliferative activity against human bronocopulmanary cancer cells with IC\textsubscript{50} 6.3 μg/mL. It also showed moderate activity against breast cancer and hepatoma with IC\textsubscript{50} 10.7 and 3.3 μg/mL respectively. Dragmacidin (7) showed\textsuperscript{7} in vitro cytotoxicity with IC\textsubscript{50} 15 μg/mL against P-388 cell lines and 1-10 μg/mL against A-549 (human lung), HCT-8 (human colon) and MDAMB (human mammary) cancer cell lines.

![Figure 1](image)

Hyrtinadine A (8) is a novel bis-indole alkaloid having 2,5-disubstituted pyrimidine skeleton. It was isolated\textsuperscript{8} from an Okinawan marine sponge of the Hyrtios genus. This compound exhibited in vitro cytotoxic activity against murine leukemia L1210 cells with IC\textsubscript{50} 1 μg/mL and human epidermoid carcinoma KB cells with IC\textsubscript{50} 3 μg/mL.
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There are two reports available for the synthesis of Hyrtinadine A (8) which are shown below.


\[
\begin{array}{c}
\text{Br} \quad \text{N} = \text{N} \quad \text{Cl} \quad \xrightarrow{\text{R}_3\text{In, Pd Cat}} \quad \text{OH} \quad \text{HO} \\
\text{HN} \quad \text{N} = \text{N} \quad \text{HN} \quad \text{NH} \\
\end{array}
\]

2. Muller, J. J. et al (2011)\(^{10}\)

\[
\begin{array}{c}
\text{R} \quad \text{N} \quad \text{Boc} \quad \xrightarrow{\text{1) HB, Et}_3\text{N, Pd(PPh}_3)_4, \text{dioxane}} \quad \text{OH} \quad \text{HO} \\
\text{HN} \quad \text{N} = \text{N} \quad \text{HN} \quad \text{NH} \\
\text{HN} \quad \text{N} = \text{N} \quad \text{HN} \quad \text{NH} \\
\text{HN} \quad \text{N} = \text{N} \quad \text{HN} \quad \text{NH} \\
\end{array}
\]

Present plan

A new short retrosynthetic plan was envisioned for hyrtinadine A, starting from 5-hydroxy indole-3-aldehyde which is shown in Scheme 1.
Results and Discussion

In the beginning, it was planned to carry out a pilot synthetic scheme, starting with an unsubstituted indole-3-aldehyde to produce an analogue of hyrtinadine A and subsequently, it could be implemented for the target molecule 8. According to the retrosynthetic scheme, the synthesis started with indole-3-aldehyde 9 (Scheme 2). In the beginning compound 9a was prepared in situ using Henry reaction of aldehyde 9 with nitromethane in presence of ammonium acetate as a base. Further, confirming the formation of new product on TLC, without isolating product 9a, some more ammonium acetate was added to the reaction mixture. After refluxing the reaction mixture for 2 hours, the reaction was worked up to get a solid. Column chromatographic separation furnished a pale yellow solid in 95% yield, having M. p. 95 °C which was characterized by analytical and spectral data. From this data structure 10 was assigned to this product. In HRMS it showed molecular ion peak at 272.0642 for C_{11}H_{11}N_{3}NaO_{4} (M+Na). $^1$H NMR (Figure 2) showed multiplates at $\delta$ 4.56 for one proton, at $\delta$ 4.99-5.03 and $\delta$ 5.09-5.13 for protons of two methylene group. Five aromatic protons were resonating between $\delta$ 7.02-7.69. A broad singlet at $\delta$ 11.15 for NH proton was also seen. $^{13}$C NMR (Figure 3) displayed singlets at $\delta$ 33.88 and 77.09 for methine and methylene carbons respectively and remaining eight carbons were resonating at appropriate positions. All the data was consistent with the structure 10 and with the reported values. The formation of product 10 can be explained as the initial formation of nitrostyrene 9a in the Henry reaction and further Michael addition of nitromethane on nitrostyrene 9a. We have modified the reported
method\textsuperscript{11} by using different base and nitromethane itself as a solvent. The yield in the modified method was shown to be very good (92\%) as compared to the reported method (55\%).

The reduction of dinitro compound 10 using 10\% Pd/C in methanol yielded diamine 11. This diamine was characterized immediately after work up due to its instability and used for further reaction without purification. The NMR of diamine 11 was taken in deuterated methanol due to its poor solubility in usual solvents. \textsuperscript{1}H NMR (Figure 4) showed a doublet for four protons of two methylene groups at $\delta$ 2.74-2.76 with $J = 6.4$ Hz, multiplate for one methine proton at $\delta$ 2.79-2.86 and five aromatic protons between $\delta$ 6.91-7.49. \textsuperscript{13}C NMR (Figure 5) exhibited singlets at 44.36 and 44.91 for aliphatic carbons and eight singlets in aromatic region. All NMR data was consistent with the reported\textsuperscript{11} values.

\begin{center}
\begin{tikzpicture}[scale=0.8]
  \node (start) at (0,0) {$\text{CHO}$};
  \node (reaction1) at (1,0) {CH$_3$NO$_2$};
  \node (reaction2) at (2,0) {NH$_4$OAc, reflux, 3h};
  \node (reaction3) at (3,0) {NH$_4$OAc, reflux, 3h, 92\%);
  \node (reaction4) at (4,0) {10% Pd/C, H$_2$, MeOH, 2h, 90\%};
  \node (product1) at (5,0) {9a};
  \node (product2) at (6,0) {10};
  \node (product3) at (7,0) {11};

  \draw [->] (start) -- (reaction1);
  \draw [->] (reaction1) -- (reaction2);
  \draw [->] (reaction2) -- (reaction3);
  \draw [->] (reaction3) -- (reaction4);
  \draw [->] (reaction4) -- (product1);
  \draw [->] (product1) -- (product2);
  \draw [->] (product2) -- (product3);
  \draw [->] (product3) -- (start);

  \node at (1.5,-1) {9};
  \node at (2.5,-1) {9a};
  \node at (3.5,-1) {10};
  \node at (4.5,-1) {11};

  \node at (0.5,-2) {$\text{CHO}$};
  \node at (1.5,-2) {CH$_3$NO$_2$};
  \node at (2.5,-2) {NH$_4$OAc, reflux, 3h};
  \node at (3.5,-2) {NH$_4$OAc, reflux, 3h, 92\%};
  \node at (4.5,-2) {10% Pd/C, H$_2$, MeOH, 2h, 90\%};
  \node at (5.5,-2) {9a};
  \node at (6.5,-2) {10};
  \node at (7.5,-2) {11};

  \node at (0.5,-3) {\textcolor{red}{\textbf{Scheme 2}}};
\end{tikzpicture}
\end{center}

In order to get tetrahydropyrimidine ring, diamine was treated with different types of electrophiles as shown below in Scheme 3.

\begin{center}
\begin{tikzpicture}[scale=0.8]
  \node (substrate1) at (0,0) {11};
  \node (electrophile1) at (1,0) {R};
  \node (product4) at (2,0) {12};

  \node at (0.5,-1) {NH$_2$NH$_2$};
  \node at (1.5,-1) {R = CHO, COOH, CN};
  \node at (2.5,-1) {\textcolor{red}{\textbf{Scheme 3}}};

  \draw [->] (substrate1) -- (electrophile1);
  \draw [->] (electrophile1) -- (product4);

  \node at (0.5,-2) {11};
  \node at (1.5,-2) {R};
  \node at (2.5,-2) {12};
\end{tikzpicture}
\end{center}
Initially, diamine was treated with indole-3-aldehyde (9) in methanol at reflux condition (Scheme 4). The reaction was monitored by TLC and continued up to 48 hours. But, starting was recovered from this reaction.

Then, we thought to use protected indole-3-aldehyde instead of indole-3-aldehyde (9). Thus, N-benzene sulphonyl protected aldehyde 13 was synthesized from aldehyde 9 using benzene sulphonyl chloride in presence of KOH as a base in DMSO (Scheme 5). The $^1$H NMR (Figure 6) showed singlet for aldehyde group at $\delta$ 10.10 and ten signals for protons in aromatic region. $^{13}$C NMR (Figure 7) displayed aldehydic carbon at $\delta$ 185.31 and twelve singlets for remaining carbons at appropriate positions. The spectral data was consistent with reported$^{12}$ values.

Now, aldehyde 13 was reacted with diamine 11 in methanol at reflux condition (Scheme 6). The reaction was monitored by TLC, a newly formed compound was purified by column chromatography to get a solid product. $^1$H NMR spectrum (see expt. section of chapter 1) showed a quintet for two protons at $\delta$ 7.24 with $J$ = 7.27 Hz, two doublets at $\delta$ 7.50-7.53 with $J$ = 8.11 Hz and at $\delta$ 8.08-8.11 with $J$ = 7.15 Hz for one proton each, two singlets at $\delta$ 8.29 and $\delta$ 9.94 for one proton each and broad singlet at $\delta$ 12.14 for one proton. $^{13}$C NMR (see expt. section of chapter 1) displayed a singlet at $\delta$ 185.40 and eight singlets between112.85-138.89. From the spectral data, the compound confirmed as indole-3-aldehyde (9). From this observation, it was found that the deprotection of -N-SO$_2$Ph has taken place instead of cyclization.
Now, benzyl protection was selected as it is removed under hydrogenation conditions. The benzyl protected aldehyde 14 was synthesized in 93%, using benzyl bromide, NaH in DMF (Scheme 7). $^1$H NMR (Figure 8) showed a singlet for methylene protons at $\delta$ 5.36, a singlet at $\delta$ 10.00 for aldehydic proton and ten signals for remaining protons in aromatic region. $^{13}$C NMR (Figure 9) showed singlet at $\delta$ 50.29 for methylene carbon, singlet at $\delta$ 185.20 for aldehyde carbonyl group and twelve singlets for remaining aromatic carbons. The spectral data was consistent with reported $^{13}$ values.

This aldehyde 14 was treated with diamine in methanol and refluxed for 48 hours but no new spot was seen from TLC and starting was recovered (Scheme 8).

Further, different acidic and basic conditions were tried for the reactions of the aldehydes 9 and 14 with diamine 11 which are summarized in the Table 1.
Unfortunately, from all the reactions, product could not be obtained and starting was recovered.

**Table 1.** Acidic and basic reaction conditions for reaction of aldehydes 9 and 14 with diamine 11

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Catalysts</th>
<th>Solvents</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>MeOH, EtOH, t-BuOH</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>p-TSA</td>
<td>MeOH, EtOH, t-BuOH</td>
<td>0 °C, reflux, microwave</td>
</tr>
<tr>
<td>3</td>
<td>H$_2$SO$_4$</td>
<td>MeOH, EtOH, t-BuOH</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Diacetoxy benzene</td>
<td>MeOH, EtOH, t-BuOH</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>amberlyst 15</td>
<td>MeOH, EtOH, t-BuOH</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Fe/MgO</td>
<td>t-BuOH</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>SnCl$_2$</td>
<td>MeOH, EtOH, t-BuOH</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CoCl$_2$</td>
<td>MeOH, EtOH, t-BuOH</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>K$_2$CO$_3$ and I$_2$</td>
<td>MeOH, EtOH, t-BuOH</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>KOH</td>
<td>MeOH, EtOH, t-BuOH</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>--</td>
<td>DMSO, DMF</td>
<td>rt to 90 °C</td>
</tr>
</tbody>
</table>

As, no product was obtained by changing the reagents as well as conditions, it was planned to use nucleophiles other than aldehydes. Therefore the use of indole-3-caboxylic acid was envisaged. The acid 16 was synthesized from indole by treating with trifluoroacetic acid in DMF, followed by basic hydrolysis using NaOH in water (Scheme 9). Two broad singlets at $\delta$ 11.87 and $\delta$ 11.7 for –COOH and -NH and five signals for remaining protons were seen in $^1$H NMR (Figure 10). $^{13}$C NMR (Figure 11) showed singlet at $\delta$ 165.9 for carboxylic carbon and eight singlets for remaining carbons in aromatic region. The spectral values were matching with the reported values of indole-3-caboxylic acid (16).
Then, indole-3-caboylic acid (16) was reacted with diamine 11 in 4N HCl in water (Scheme 10). The reaction was monitored by TLC which showed mixture of many spots.

Further, benzyl protected acid 17 was synthesized from benzyl protected aldehyde 14 by oxidation with KMnO₄ in acetone water mixture (Scheme 11). NMR showed disappearance of aldehydic signal and appearance of -COOH signal (broad singlet at δ 12.1 in ¹H NMR (Figure 12) and singlet at δ 166 in ¹³C NMR (Figure 13)). The spectral data was consistent with reported values.

The acid 17 was reacted with diamine 11 in acidic condition (Scheme 12) as mentioned above. Again a complex mixture was obtained in this reaction also. Thus, by using acid instead of aldehyde as an electrophile, formation of product could not be achieved.
There are many reports\textsuperscript{16} in literature for the formation of imidazoline skeleton using diamine and nitrile. Therefore, commercially available indole-3-carbonitrile was treated with diamine 11 in EtOH in the presence of \( p \)-TSA and the reaction mixture was refluxed thermally and also by sonication condition (Scheme 13). However, formation of new product was not observed.

![Scheme 13](image)

Concurrently, a literature report\textsuperscript{17} for the synthesis of indole system from oxindole, using LAH was found. Therefore we envisioned to use an aldehyde 21 having oxindole moiety. The aldehyde 21 was synthesized from oxindole 20 by reacting with ethyl formate in presence of NaOMe as a base (Scheme 14). It showed singlet for aldehyde group at \( \delta \) 10.10 and \( \delta \) 184.5 in \(^1\)H and \(^{13}\)C NMR respectively (Figure 14 and 15 respectively). Remaining signals were found at appropriate positions.

![Scheme 14](image)

Further, aldehyde 21 was reacted with diamine 11 in MeOH reflux condition (Scheme 15), a new compound was isolated after chromatographic separation. The NMR of newly formed compound was taken which showed disappearance of aldehydic signal. \(^1\)H NMR (Figure 16) showed singlet at \( \delta \) 3.55 for two protons and multiplates for four protons in aromatic region from \( \delta \) 6.89 to 7.27 along with one broad singlet at \( \delta \) 9.04. \(^{13}\)C NMR (Figure 17) displayed singlets at \( \delta \) 36.24, 109.76, 122.30, 124.57, 125.26, 127.90, 142.55, and 177.94. From the NMR data, the compound was found to be decarbonylated compound, which was oxindole (20). The NMR data was consistent with the reported\textsuperscript{18} NMR of oxindole.
Several attempts carried out for the synthesis of tetrahydro-pyrimidine ring were not successful. This was somewhat consistent with an earlier report indicating less reactivity of the diamine. Therefore, a new route was envisioned which included the initial incorporation of two indole ring and further cyclization. The retrosynthetic plan was shown below (Scheme 16).

The synthesis was started indole-3-carboxylic acid (16, Scheme 17). The amide formation between 1H-indole-3-carboxylic acid 16 and 2,2-dimethoxyethanamine using N,N'-dicyclohexylcarbodiimide (DCC) as a coupling reagent in DCM gave N-(2,2-dimethoxyethyl)-1H-indole-3-carboxamide (22) in 85%. The 1H NMR (Figure 18) showed a singlet for six methyl protons at $\delta$ 3.40, a doublet for methylene protons at $\delta$ 3.48-3.50 with $J$= 5.3 Hz, a triplet for a methine proton at $\delta$ 4.56 with $J$= 5.6 Hz, signals for five aromatic protons, and a broad singlet for -NH at $\delta$ 7.81. 13C NMR (Figure 19) showed singlets at $\delta$ 40.8 for methylene carbon and at 55.2 for methyl
carbon. The singlet for methine carbon was very much deshielded and overlapped with the signals of aromatic carbons. A singlet was also seen at δ 160 for carbonyl carbon of amide group. All the spectral data confirmed the formation of the product 22. The removal of dimethyl acetal group in the compound 22 by 6N HCl in THF gave unstable aldehyde (23) in 70% yield (crude) which was used immediately after the work up for further transformation. The Henry reaction of aldehyde 23 was performed however the reaction mixture decomposed. The further attempts for the Henry reaction at different temperature are ongoing in our lab.

Unfortunately, various attempts towards the synthesis of analogue of the target molecule Hyrtinadine A 8 were unsuccessful. Due to lack of time, the target was handed over to someone from our laboratory.
Chapter 3: Section B

Conclusion

The various attempts towards the synthesis of analogue of Hyrtinadine A were performed. The modification for the synthesis of dinitro compound 10 to enhance the yield was achieved and a new compound 22 was synthesized and characterized. Further work is in progress in our laboratory.
Experimental Section

3-(1,3-dinitropropan-2-yl)-1H-indole (10)

To a suspension of aldehyde 9 (1 g, 6.89 mmol) in nitromethane (25 mL) was added ammonium acetate (0.98 g, 10.3 mmol). The mixture was refluxed for 3 h. The formation of nitrostyrene was visualized on TLC. After total conversion of aldehyde 9 into nitrostyrene on TLC, ammonium acetate (0.98 g, 10.3 mmol) was added and reaction mixture was refluxed for further 3 h. Then reaction mixture was concentrated, water (50 mL) was added to the residue and extracted with CH2Cl2 (3×20 mL). The organic layers were separated, washed with brine and dried over Na2SO4. After concentration, the crude product was purified by column chromatography (pet ether: ethyl acetate) to give Michael adduct (10) as pale yellow solid (1.57 g, 92%). M. p. 98 °C.

1H NMR (500 MHz, DMSO-d6): δ 4.51-4.59 (m, 1H), 4.98-5.04 (m, 2H), 5.08-5.14 (m, 2H), 7.04 (ddd, J = 7.93, 7.02, 0.92 Hz, 1H), 7.12 (td, J = 7.55, 1.07 Hz, 1H), 7.33-7.43 (m, 2H), 7.67-7.69 (d, J = 7.93 Hz, 1H), 11.15 (brs., 1H).

13C NMR (125 MHz, DMSO-d6): δ 33.88, 77.09, 108.56, 111.78, 118.17, 119.06, 121.54, 123.87, 125.74, 136.11.

HRMS (ESI): m/z calcd for C11H11N3NaO4 (M+Na)+, 272.0642; found, 272.0642.

2-(1H-indol-3-yl)propane-1,3-diamine (11)

In a 100 mL round-bottom flask, the dinitro compound (10) (1.00 mmol) was dissolved in MeOH (10 mL) and 10% Pd/C (0.20 mmol) was added (carefully), to which a H2 balloon was connected. The resulting suspension was stirred at room temperature for 4 h (TLC) and the mixture filtered through Celite and washed with MeOH (5 mL). The solvent was evaporated under reduced pressure to afford the diamine 11, which was used further without further purification.

1H NMR (300 MHz, Methanol-d4): δ 2.74-2.76 (d, J = 6 Hz, 4H), 2.79-2.86 (m, 1H), 6.90-6.97 (m, 1H), 7.00-7.06 (m, 2H), 7.36 (d, J = 8.21 Hz, 1H), 7.46-7.49 (d, J = 7.62 Hz, 1H).
$^{13}$C NMR (75 MHz, Methanol-$d_4$): $\delta$ 44.36, 44.91, 112.89, 114.84, 119.95, 120.06, 122.85, 124.15, 128.06, 138.34.

**N-Benzene sulfonyl-3- indolecarbaldehyde (13)**

The KOH pellets (1.1 g, 0.02 mol) were added to DMSO (20 mL) and the mixture was vigorously stirred. After 15-20 minutes, indole 3-carbaldehyde (9) (1.45 g, 0.01 mol) was added to it. The solution turned faint pink. After stirring for one and half hour, benzenesulphonyl chloride (2.5 mL, 0.02 mol) was added drop wise. The solution was stirred overnight. After completion of the reaction, ice cold water was added and extracted with CH$_2$Cl$_2$. The solvent was evaporated and the residue was chromatographed on silica gel using pet ether-ethyl acetate as an eluent to give the product. M.p. 156 °C

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.32-7.45 (m, 2H), 7.47-7.55 (m, 2H), 7.57-7.64 (m, 1H), 7.92-8.01 (m, 3H), 8.21-8.29 (m, 2H), 10.10 (s, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 113.15, 122.43, 122.57, 125.09, 126.22, 126.36, 127.09, 129.67, 134.70, 135.15, 136.14, 137.25, 185.31.

**1-benzyl-1H-indole-3-carbaldehyde (14)**

To a stirred solution of aldehyde 9 (1 g, 3.44 mmol) in dry DMF (15 ml) at 0°C was added NaH (60% dispersion in mineral oil, 0.330 g, 8.6 mmol). The mixture was stirred for 30 min at 0 °C and allowed to warm to 10 °C. Then benzyl bromide (0.409 mL, 3.44 mmol) was added and the mixture was stirred for 2 h. It was added water (25 mL). The solid was precipitated out, which was filtered, washed with water, dried which gave product 14. M.p. 107 °C

$^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 5.54 (s, 2H), 7.22-7.35 (m, 7H), 7.55-7.62 (m, 1H), 8.09-8.17 (m, 1H), 8.47 (s, 1H), 9.95 (s, 1H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 49.82, 111.41, 117.42, 121.11, 122.58, 123.64, 124.83, 127.35, 127.80, 128.73, 136.77, 136.98, 141.01, 184.72.
Procedure for the reaction of diamine 11 and aldehyde 9

Diamine (11, 1 equivalent) was dissolved in (15 mL) methanol/ethanol/t-BuOH. The solution of indole-3-aldehyde (9, 1.2 equivalent) in the same solvent was added to the above solution at various temperatures (0 °C, rt) and heated to reflux. The reaction was monitored by TLC and continued up to 48 hours, and then solvent was removed under vacuum. The ethyl acetate (10 mLx2) was added to the residue to remove alcohol and residual water from the crude mixture. The residue was chromatographed on silica gel. The reactions using aldehydes 13, 14, 21 were also carried out in similar fashion, wherever needed the catalysts and microwave conditions were used.

1H- indole-3-carboxylic acid (16)

To the solution of indole (2.34 g, 20 mmol) in DMF (10 ml), trifluoroacetic anhydride (4.2 mL, 30 mmol) was added drop wise at 0 °C. After stirring for 3 h at rt, water was added and the pink solid was filtered. The collected solid was treated with 20% NaOH (40 ml, 0.2 mmol) at 50 °C overnight. After cooling to rt, the solution was extracted with diethyl ether. The aqueous phase was acidified with conc. HCl and the product was filtered. Compound 16 was obtained as a brownish solid (2.47 g, 77%). M.p. 194 °C (decomposed).

\[ ^1H \text{ NMR (500 MHz, DMSO-d}_6\]): \delta 7.10-7.22 (m, 2H), 7.39-7.48 (m, 1H), 7.89-7.90 (d, J = 2.75 Hz, 1H), 8.03-8.13 (m, 1H), 11.30-11.91 (m, 2H). \]

\[ ^{13}C \text{ NMR (125 MHz, DMSO-d}_6\)] δ ppm 107.36, 111.65, 120.61, 121.75, 121.76, 125.79, 131.43, 136.19, 166.13

1-Benzyl-1H- indole-3-carboxylic acid (17)

To a solution of indole 3-aldehyde (9) (420 mg, 1.78 mmol) in acetone-water mixture (80 mL, 1:1 v/v) was added KMnO₄ (1.12 mg, 7.12 mmol). The mixture was stirred for 3 h, filtered on celite and concentrated under vacuum to remove the organic solvent. The resulting aqueous solution was cooled and acidified with HCl (conc.) to afford a white precipitate, which was collected by filtration and dried to provide pure carboxylic acid (17) (358 mg, 80%). M. p. 183 °C.
1H NMR (300 MHz, DMSO-\textit{d}_6): \( \delta \) 5.34 (s, 2H), 7.14-7.19 (m, 2H), 7.21-7.25 (m, 2H), 7.27-7.36 (m, 4H), 7.89 (s, 1H), 8.17-8.24 (m, 1H).

13C NMR (75 MHz, DMSO-\textit{d}_6): \( \delta \) 50.11, 107.33, 109.82, 121.25, 122.21, 126.61, 127.52, 128.38, 134.38, 135.54, 136.22, 166.38.

**Procedure for the reaction of diamine 11 and acid 16**

Diamine 11 (1 equivalent) and acid 16 (1 equivalent) were added 4N HCl (50 mL) and content were refluxed with stirring for 5 h. The mixture was treated with aqueous sodium bicarbonate solution until pH 9, the solid precipitated out was filtered off, washed with ether which was purified by column chromatography using pet ether and ethyl acetate as eluent. The same procedure was repeated for acid 17.

**Procedure for the reaction of diamine 11 and nitrile 19**

To a mixture of diamine (11, 1.2 equivalent) in EtOH (20 mL) was added nitrile (19, 1.2 equivalent). The mixture was heated under reflux/sonicated for 0.5 h to 10 h and cooled to room temperature. The reaction mixture was concentrated in vacuo. No product was obtained and starting was recovered from the reaction.

**2-Oxindoline-3-carbaldehyde (21)**

\[
\begin{align*}
\text{CHO} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\]

Sodium methoxide solution was prepared from sodium (0.18 g) and 5 mL of dry methanol, which was added oxindole (0.5 g, 3.75 mmol) and ethyl formate (0.8 g, 57.56 mmol) and mixture was refluxed for 1 h. At ambient temperature, reaction mass was added to ice-cold water with stirring and pH was adjusted to 3 by adding 1:1 conc HCl-water. The stirring was continued for 30 min and resultant solid was filtered on Buchner funnel under vacuum, dried to give this aldehyde in 95%. M.p. 205 °C

1H NMR (500 MHz, METHANOL-\textit{d}_4): \( \delta \) ppm 4.90 (s, 1H), 6.87-6.88 (d, \( J = 7.93 \) Hz, 1H), 6.95-6.99 (m, 1H), 7.06-7.11 (m, 1H), 7.63-7.64 (d, \( J= 7.63 \) Hz, 1H), 7.96 (s, 1H).

13C NMR (125 MHz, METHANOL-\textit{d}_4): \( \delta \) 47.91, 106.61, 108.85, 121.33, 122.08, 122.92, 125.71, 137.95, 156.04, 172.59.

HRMS (ESI): m/z calcd for C9H8NO2 (M+H)+, 162.0550; found, 162.0548.
**Oxindole (20)**

M.p. 126 °C

\[ \delta 3.57 \text{ (s, 2H)}, 6.91-6.93 \text{ (d, } J = 7.63 \text{ Hz, 1H)}, 7.01-7.07 \text{ (m, 1H)}, 7.21-7.27 \text{ (m, 2H)}, 8.82 \text{ (brs., 1H)}. \]

\[ \delta 3.60, 109.70, 122.31, 124.60, 125.26, 127.90, 142.47, 177.71. \]

**N-(2,2-dimethoxyethyl)-1H-indole-3-carboxamide (22)**

In 100 ml round bottom flask, corresponding amine (1.7 gm) was taken with 50 ml DCM cooled at at 0 °C. Then DCC (1.6 gm) was added and stirred for 15 min. In the next step indole 3-acid (0.7 gm) was added at 0 °C and reaction stirred at same temp for one hr. Then temperature was increased to rt and stirring was continued for 6 h. The precipitate was filtered, washed with DCM, evaporated and purified by column chromatography using pet ether-ethyl acetate as an eluent to give the product as a white solid, 85%. M.p. 127 °C

\[ \delta 3.43 \text{ (s, 6 H)} 3.51-3.52 \text{ (d, } J = 5.49 \text{ Hz, 2 H)} \]

\[ 4.59 \text{ (t, } J = 5.49 \text{ Hz, 1 H)} 4.63 \text{ (s, 1 H)} 7.17 \text{ (m, 2 H)} 7.42 \text{ (dt, } J=8.01, 1.03 \text{ Hz, 1 H)} \]

\[ 7.89 \text{ (s, 1 H)} 8.07 \text{ (dt, } J = 8.09, 0.99 \text{ Hz, 1 H)} \]

\[ \delta 42.30, 54.81, 104.47, 111.80, 112.98, 121.71, 122.17, 123.64, 127.14, 129.39, 138.23, 168.72. \]

HRMS (ESI): m/z calcd for C_{13}H_{17}N_{2}O_{3} (M+H)^{+}, 249.1234; found, 249.1238.

**N-(2-oxoethyl)-1H-indole-3-carboxamide (23)**

A solution of compound 23 (0.2 g, 0.89 mol) in THF (20 mL) and 6N HCl (20 mL) was stirred for 18 h and monitored by TLC. Then THF was removed under vacuum, brine (20 mL) was added and reaction mixture was extracted with DCM: MeOH (9:1). The combined organic extracts were dried over Na_{2}CO_{3} and concentrated and used without purification for Henry reaction as described above for compound 10.
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$^1$H and $^{13}$C NMR spectra of products

Figure 2. $^1$H-NMR spectrum of 10 (500MHz, DMSO-$d_6$)

Figure 3. $^{13}$C-NMR spectrum of 10 (125MHz, DMSO-$d_6$)
Figure 4. $^1$H-NMR spectrum of 11 (300MHz, Methanol-$d_4$)

Figure 5. $^{13}$C-NMR spectrum of 11 (75MHz, Methanol-$d_4$)
Figure 6. $^1$H-NMR spectrum of 13 (500MHz, CDCl$_3$)

Figure 7. $^{13}$C-NMR spectrum of 13 (125MHz, CDCl$_3$)
Figure 8. $^1$H NMR spectrum of 14 (500MHz, DMSO-$d_6$)

Figure 9. $^{13}$C NMR spectrum of 14 (125MHz, DMSO-$d_6$)
Figure 10. $^1$H-NMR spectrum of 16 (500MHz, DMSO-$d_6$)

Figure 11. $^{13}$C-NMR spectrum of 16 (125MHz, DMSO-$d_6$)
Figure 12. $^1$H-NMR spectrum of 17 (500MHz, DMSO-$d_6$)

Figure 13. $^{13}$C-NMR spectrum of 17 (125MHz, DMSO-$d_6$)
Figure 14. $^1$H-NMR spectrum of 21 (500MHz, Methanol-$d_4$)

Figure 15. $^{13}$C-NMR spectrum of 21 (125MHz, Methanol-$d_4$)
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**Figure 16.** $^1$H-NMR spectrum of 20 (500MHz, CDCl$_3$)

**Figure 17.** $^{13}$C-NMR spectrum of 20 (125MHz, CDCl$_3$)
Figure 18. $^1$H NMR spectrum of 22 (500MHz, Methanol-$d_6$)

Figure 19. $^{13}$C NMR spectrum of 22 (125MHz, Methanol-$d_6$)
References