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Concise and Efficient Total Synthesis of Bioactive Natural Product Pegamine

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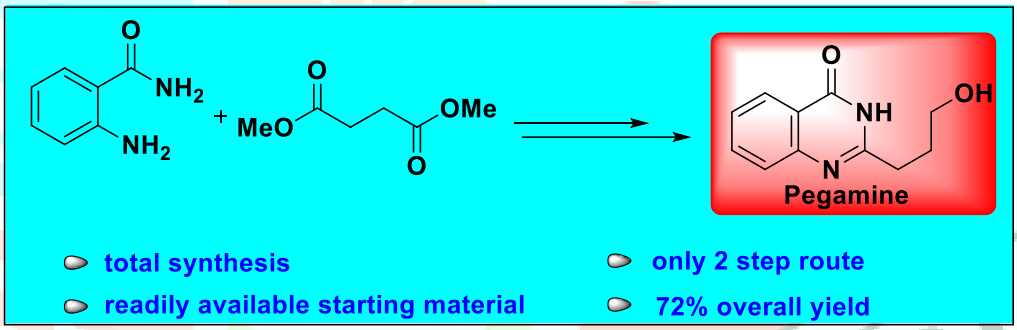
Abstract: A novel two step total synthesis of natural product Pegamine was successfully carried out from readily available, cheap starting material in 72% overall yield.

Graphical Abstract:



1. Introduction:

Enormous quantities of quinazolinone alkaloids have been confined from various plants, creatures, and microorganisms and blended taking into account their grounded pharmacological activities.[1] Development of new rich manufactured procedures to these bioactive quinazolinone alkaloids and their antecedents is a difficult assignment of current interest.[2] Pegamine [2-(3-hydroxypropyl)- quinazolin-4(1H)-one, 5], deoxyvasicinone [2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one,], and (-)-vasicinone [2,3-dihydro-3(S) hydroxypyrrolo[2,1-b]quinazolin-9(1H)- one,] have been disengaged as bioactive regular items. Pegamine (5) has been segregated from Peganum harmala and displays cytotoxic activity.[3] Deoxyvasicinone and (-)- vasicinone have been confined from airborne pieces of an evergreen subherbaceous bramble Adhatoda vasica. (Figure 1)

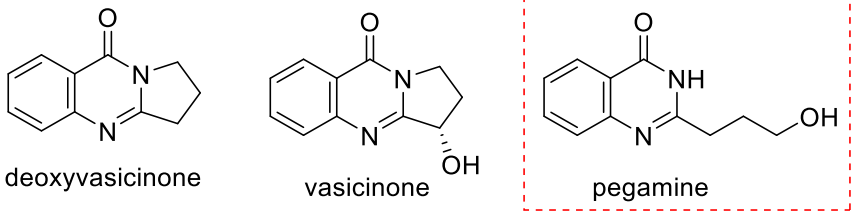


Figure 1. Natural products obtained from pegamine with qunazolinone motifs

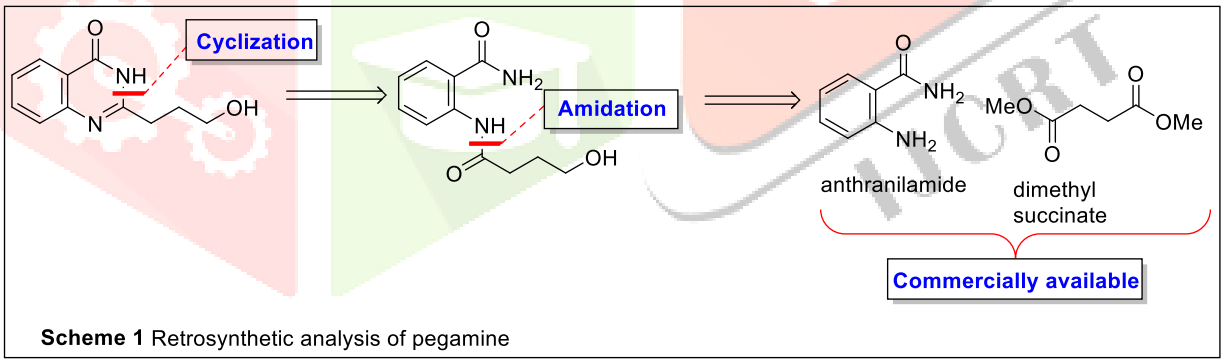
many routes to synthesise pegamine were reported in the literature. Eguchi et al synthesised (+)-vasicinone from Deoxyvasicinone via Pegamine.[4] Mhaske et al reported the synthesis of deoxyasicinone via Pegamine.[5]

Synthesis of pegamine is important not only because of its biological activities but also due to it acts as a precursor for the synthesis of other natural products like deoxyvasicinone, luotonin F etc. This fact and our previous studies[6] encouraged us to establish the new two step route for the synthesis of pegamine

2. Observations and results:

2.1. Retrosynthetic analysis:

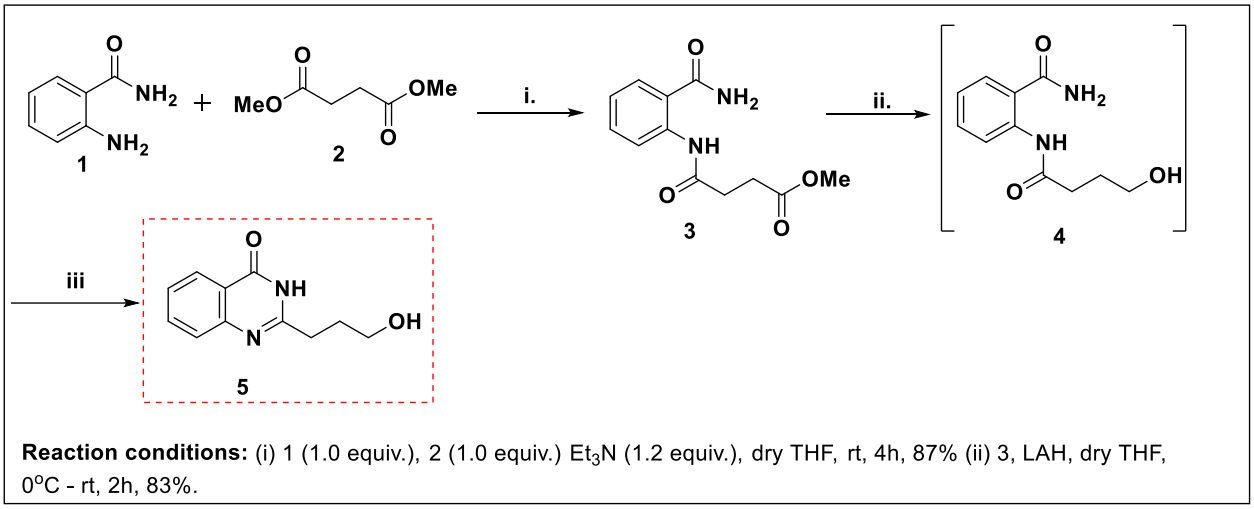
We envisioned that, Pegamine can be synthesised from the anthranilamide and dimethyl succinate amide formation reaction. This amide containing terminal ester group on reduction will provide terminal alcohol containing amide. This compound then on annulation will give us the desired product Pegamine.



Scheme 1 Retrosynthetic analysis of pegamine

2.2. Synthesis:

We began our actual synthesis from the amidation reaction between readily available cheap starting material anthranilamide and dimethyl succinate to obtain amide (3) in 87% yield. Thus obtained amide having terminal ester group was reduced to alcohol (4). This compound (4) on in situ annulation with LAH yielded the final targeted product pegamine (1) in 83% yield over 2 steps. The overall 72% yield of Pegamine was obtained.



Reaction conditions: (i) 1 (1.0 equiv.), 2 (1.0 equiv.) Et_3N (1.2 equiv.), dry THF, rt, 4h, 87% (ii) 3, LAH, dry THF, 0°C - rt, 2h, 83%.

2.3. Experimental:

Synthesis of methyl 4-((2-carbamoylphenyl)amino)-4-oxobutanoate (3):

To a dried two neck round bottom flask containing anthranilamide 1 (100 mg, 0.73 mmol) in dry THF was added dimethyl succinamide 2 (107 mg, 0.73 mmol) and stirred the reaction for 4 h at room temperature. The reaction is quenched after total consumption of starting material (checked by tlc) by cold solution of dil. HCl. The organic layer was extracted in 15 x 3 ml of ethyl acetate and dried over granular sodium sulfate. The combined organic layers were concentrated in vacuo to obtain white residue of crude product which was further purified by silica gel (mesh 100-200) gel column chromatography using eluent system of ethyl acetate:hexane (7:3, v/v) to obtain pure white crystals of amide 3 in 87% yield. mp 133-135 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.75 (s, 4H), 3.71 (s, 3H), 5.50-6.00 (bs, 1H), 6.00-6.50 (bs, 1H), 7.08 (t, *J*) 8 Hz, 1H), 7.40- 7.60 (m, 2H), 8.61 (d, *J*) 10 Hz, 1H), 11.25 (bs, 1H)

IR (Nujol) *v*max: 3358-3192, 1750, 1680, 1669 cm^{-1}

Synthesis of Pegamine 5

To the slurry of LAH (0.76 g, 20 mmol) in THF (20 mL) was added a solution of ester 5b (3.08 g, 10 mmol) in THF (30 mL) in a dropwise fashion at 0-5 °C over a period of 30 min with continuous stirring. The reaction mixture was further stirred at room temperature for 1 h. The reaction was slowly quenched with water (25 mL) and further stirred for 1 h at room temperature. Saturated ammonium chloridel solution (10 mL) was added to the reaction mixture, and then it was completely concentrated under vacuum and dried to the pump. The residue was stirred with THF (75 mL) for 1 h, and the organic layer was filtered through Celite, dried over sodium sulfate, and concentrated in vacuo. The obtained crude product was purified by silica gel column chromatography using a mixture of ethyl acetate and methanol (99:1) to furnish pegamine 5 in 92% yield as white solid. mp 164-165 °C.

1H NMR (CD_3OD, 400 MHz) δ: 2.00 (quintet, *J*) 6 Hz, 2H), 2.77 (t, *J*) 8 Hz, 2H), 3.66

(t, *J*) 6 Hz, 2H), 7.48 (t, *J*) 8 Hz, 1H), 7.63 (d, *J*) 8 Hz, 1H), 7.79 (t, *J*) 8 Hz, 1H), 8.17 (d, *J*) 8 Hz, 1H);

^{13}C NMR (CD_3OD, 100 MHz) δ: 31.3, 33.0, 62.1, 121.8, 127.1, 127.3, 127.4, 127.6, 135.9, 150.0, 159.3.

MS (m/e) 204, 187, 173, 160, 132, 119, 90, 77, 63.

IR (Nujol) vmax: 3394, 3315, 3173, 3122, 3037, 1695, 1683 cm^{-1}

Conclusion: We have successfully demonstrated the synthesis of Pegamine from readily available, cheap starting material efficiently in 2 steps with overall yield of 72%.

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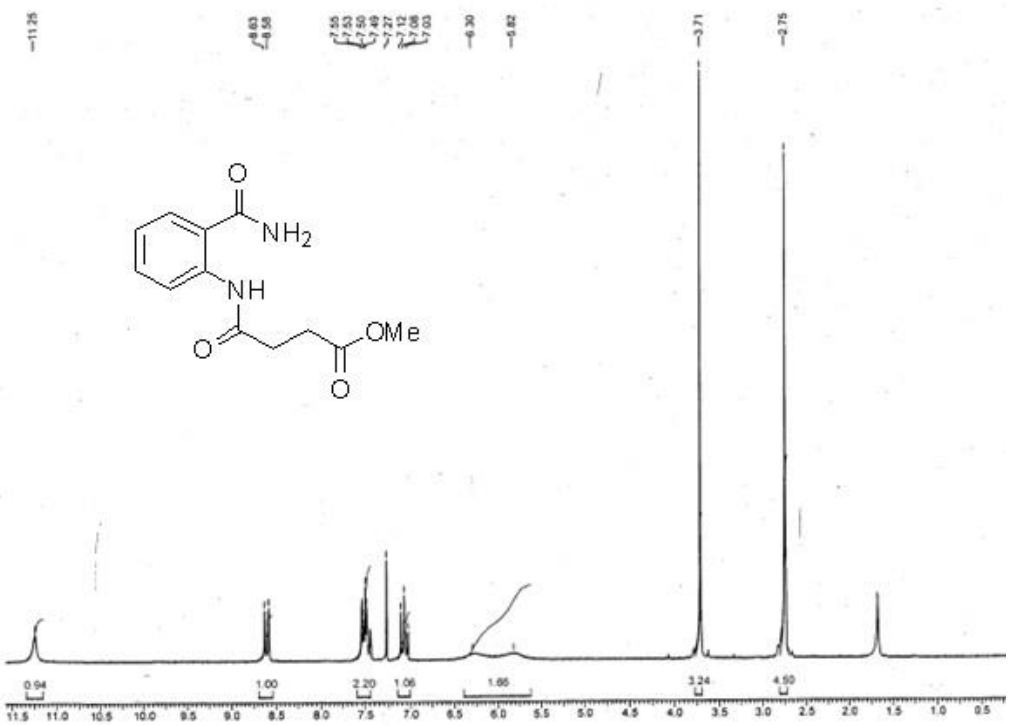
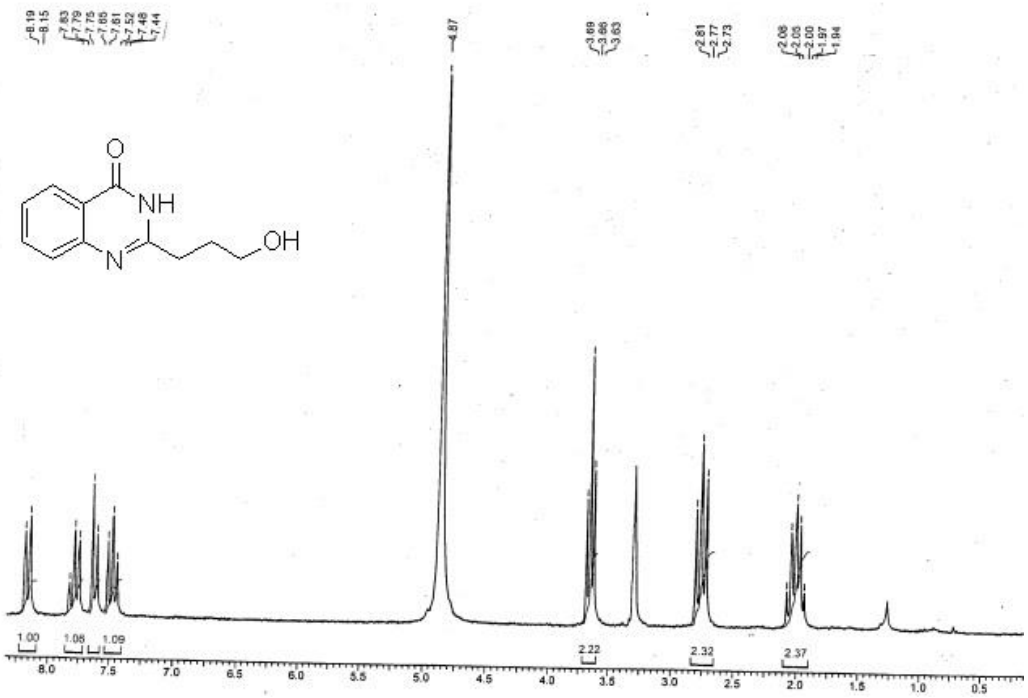
Spectra:

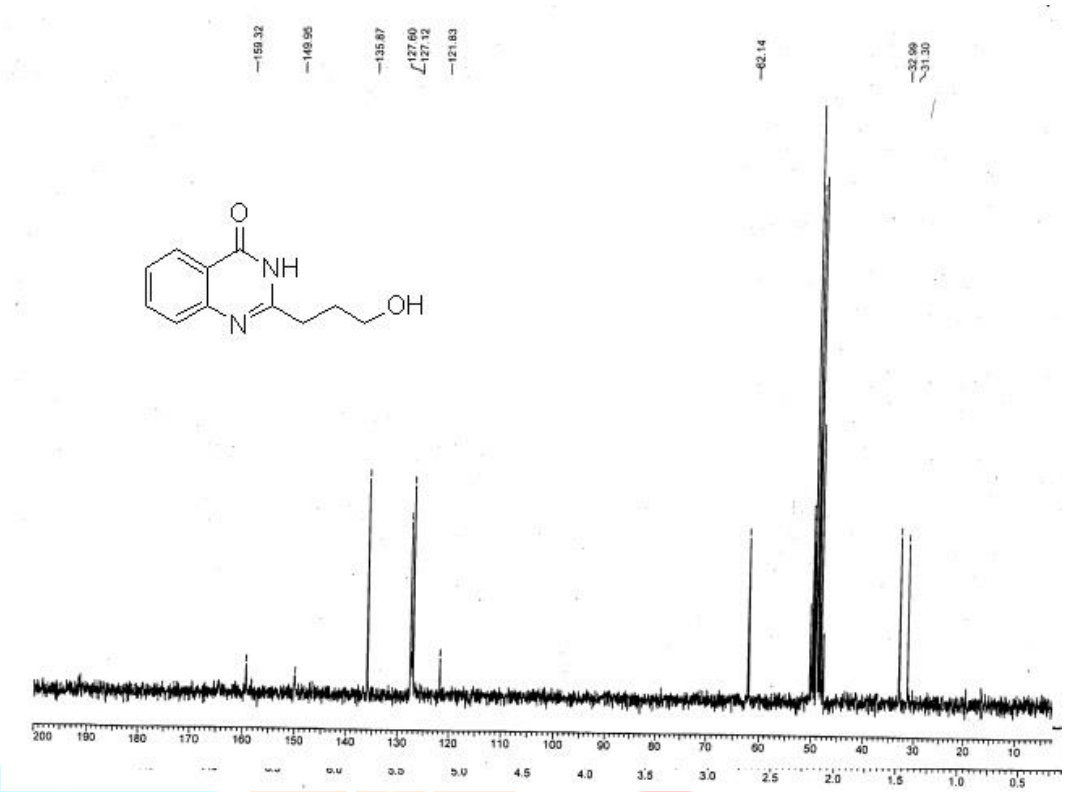
^{1}H NMR



^{1}H NMR



^{13}C NMR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149.95
135.87
127.60
127.12
121.83
62.14
32.99
31.30
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NH
N
OH
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4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5