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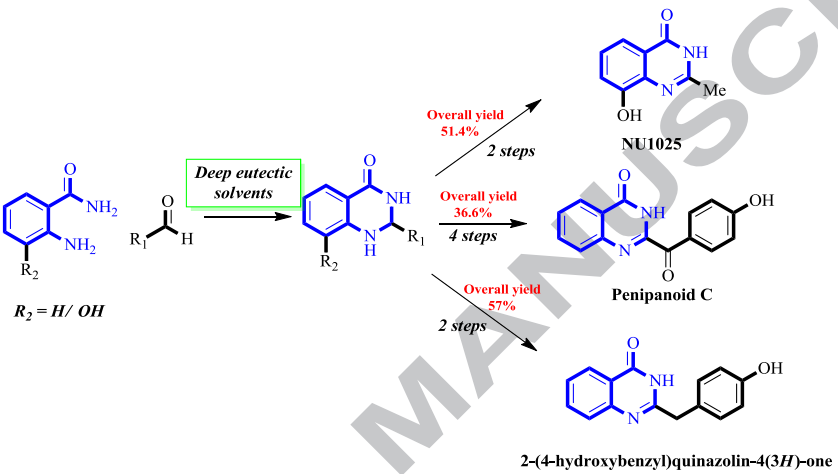

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Total synthesis of penipanoid C, 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one and NU1025

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ABSTRACT

The first total synthesis of penipanoid C and 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one is reported using a greener mild deep eutectic solvent mediated cyclization strategy with good overall yields. NU1025 drug is also synthesized using the similar protocol.

Nitrogen containing heterocyclic cores always remained as an important building block among naturally occurring alkaloids.[1] Due to their versatile pharmacological and biological properties there is always an urge for synthesis of nitrogen containing natural products.[2] Among these heterocyclic cores, quinazolinone is one of the important core that is present in a variety of naturally occurring alkaloids. The distinctive biological properties of quinazolinones like, protein tyrosine kinase inhibition, cholecystokinin inhibiton, anti-microbial, anticonvulsant, sedative, hypotensive, anti-depressant, anti-inflammatory, and anti-allergy fascinates chemists to synthesize various quinazolinone alkaloids.[3]

In 2011, Wang group isolated four new alkaloids; penipanoid A (**1**), penipanoid B (**2**), penipanoid C (**3**) and 2-(4-hydroxybenzyl) quinazolin-4(3*H*)-one (**4**) from the marine sediment-derived fungus *penicillium paneum* SD-44 (**Figure 1**).[4] Among them penipanoid B and C (**2** and **3**) were newly isolated quinazolinone alkaloids whereas alkaloid **4** was already known in literature, as Che *et al.* isolated this compound **4** along with other six alkaloids from the *Cordyceps*-colonizing fungus *Isaria farinose* in 2011 itself.[5] Later, Penipanoid C and compound **4** was again isolated from marine fungus *Penicillium oxalicum* 0312F$_1$.[6] Compound **4** was reported for its significant cytotoxic activity against the A-549 and BEL-7402 cell lines cell with IC$_{50}$ values of 17.5 and 19.8 μM, and also exhibits strong inhibitory activity on the replication of tobacco mosaic virus (TMV).[4,6]

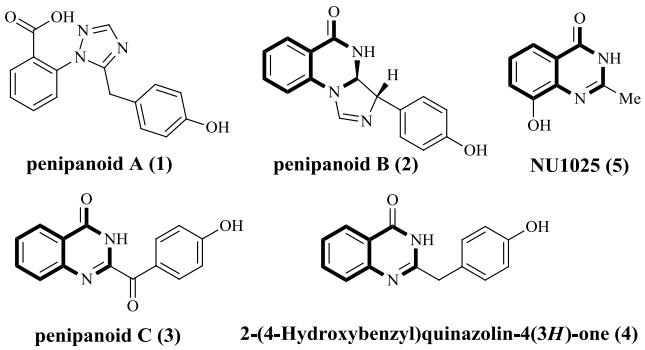

Figure 1. Structure of alkaloids isolated from the marine sediment derived fungus *Penicillium paneum* SD-44 & NU1025 drug.

Penipanoid C shows moderate inhibitory activity against TMV and human gastric cancer cell SGC-7901.[4, 5, 6] Penipanoid C was extracted in a small amount and thus tested only for antimicrobial activity against two bacteria and five plant-pathogenic fungi where it showed no activity. Hence, synthesis of these natural alkaloids were necessary due to their low abundance and wide biological spectrum.[4]

NU1025 [8-hydroxyl-2-methyl-4(3*H*)-quinazoline] (**5**, **Figure 1**) is known as a potent inhibitor of poly(ADP ribose) polymerase. NU1025 potentiate the cytotoxicity of a panel of mechanistically diverse anti-cancer agents was evaluated in L1210 cells.[7] However; in literature no synthetic report are

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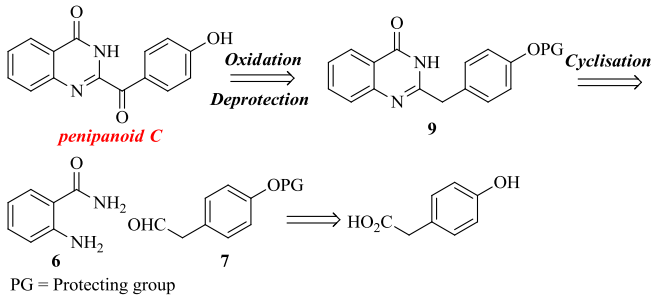
available till today for these molecules. As our group is working on the synthesis of various natural products especially on quinazolinones,[8] These alkaloids fascinated us as they are structurally related and contains the quinazolinone core (**Fig. 1**). Recently, we reported, synthesis of various quinazolinones using Deep Eutectic Solvent (DES).[9] From an environmental perspective, use of deep eutectic solvent mediated cyclization as a key step for total synthesis of alkaloids would open new directions for the scientific community. Thus, in this letter, we report the first total synthesis of penipanoid C and 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one *via* deep eutectic solvent mediated cyclization strategy.

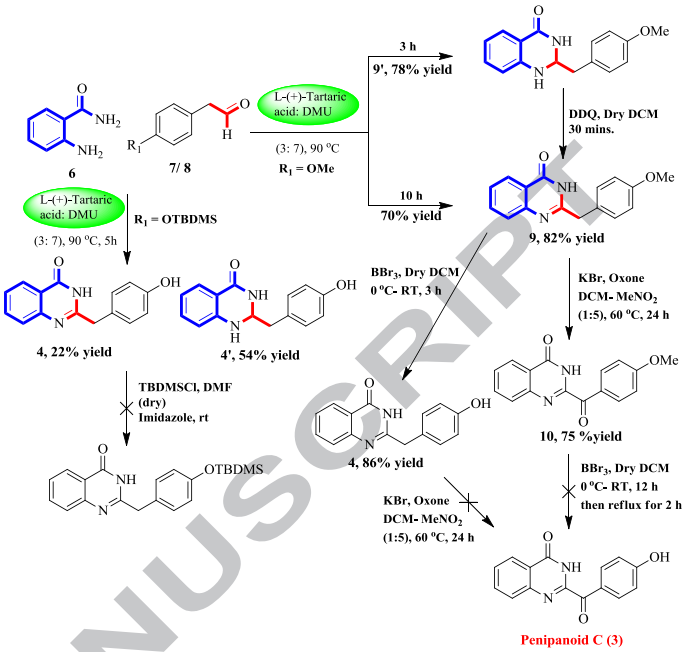
Scheme 1: Retrosynthesis of penipanoid C



Scheme 1 shows the retrosynthetic approach for penipanoid C which can be obtained from compound **9** *via* benzylic oxidation and deprotection in consecutive steps. Compound **9** can be stemmed using a cyclization reaction of commercially available anthranilimide and appropriately protected phenylacetaldehyde.

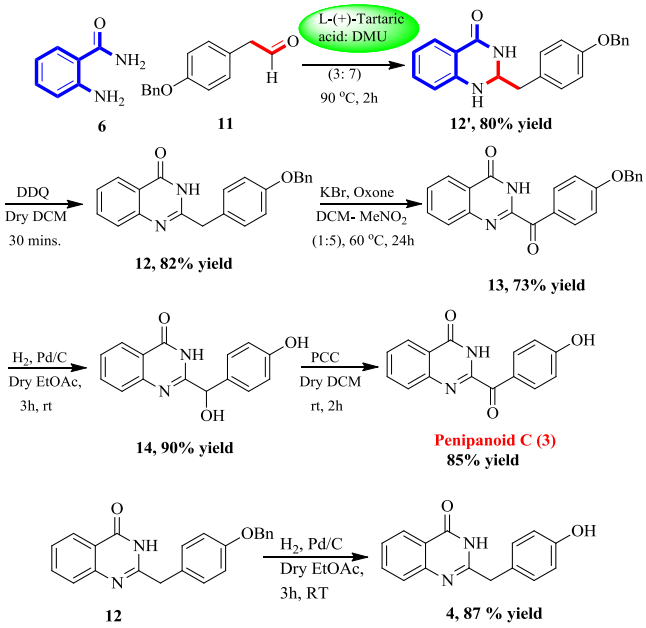
Our investigation began with the preparation of 4-methoxyphenylacetaldehyde (**7**) from 4-hydroxylphenylacetic acid by following three consecutive steps. Next, this aldehyde (**7**) was treated with anthranilamide (**6**) in the L-(+)-tartaric acid-DMU mixture (3:7) at 90 °C to obtain the 2-(4-methoxybenzyl)-2,3-dihydroquinazolin-4(1*H*)-one (**9'**) which was further converted to the aromatized product 2-(4-methoxybenzyl)quinazolin-4(3*H*)-one (**9**) with DDQ at rt. We could acquire compound **9** directly if the cyclization reaction was continued for 10h. Next, methoxy deprotection of compound **9** with BBr_3 gave the alkaloid 2-(4-hydroxybenzyl) quinazolin-4(3*H*)-one (**4**) with a good overall yield. We envisaged that the benzylic oxidation of compound **4** could have been able to furnish the penipanoid C but unfortunately direct benzylic oxidation strategy was a failure. It was the free phenolic –OH which might be the reason for this termination. Thus, we first carried out the oxidation step at the benzylic position of compound **9** with KBr/ Oxone in DCM-$MeNO_2$ solvents to obtain compound **10** in 75% yields.[10] Next, deprotection of methoxy group of compound **10** with BBr_3 to obtain penipanoid C, was a failure again. Coordination of BBr_3 with the carbonyl group might be the probable reason for this failure. Thus we modified the strategy with a different protecting group, from methoxy to tert-butyldimethylsilyl ether (-OTBDMS) (**8**). Unfortunately, when the anthranilamide (**1a**) and compound **8** was subjected to our standard cyclization condition, we obtained the corresponding TBDMS deprotected dihydroquinazolinone (**4'**) and quinazolinone (**4**) product. The acidic nature of the reaction media might be the reason for this deprotection of TBDMS group. Protection of compound **4** with TBDMS was again attempted using TBDMSCl and imidazole in dry DMF but it again went in vain. After failing for two times with two different protecting groups, we opted for a neutral and easy leaving group like benzyl.

Scheme 2: Synthesis of 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one and penipanoid C



We prepared 2-(4-(benzyloxy)phenyl)acetaldehyde (**11**) in three steps from 4-hydroxyphenylacetic acid. Next, Compound **11** and anthranilamide (**6**) were added to the L-(+) tartaric acid-DMU mixture (3:7) at 90 °C, corresponding dihydroquinazolinone (**12'**) was obtained in 80% yield.

Scheme 3: Revised synthesis of 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one and penipanoid C

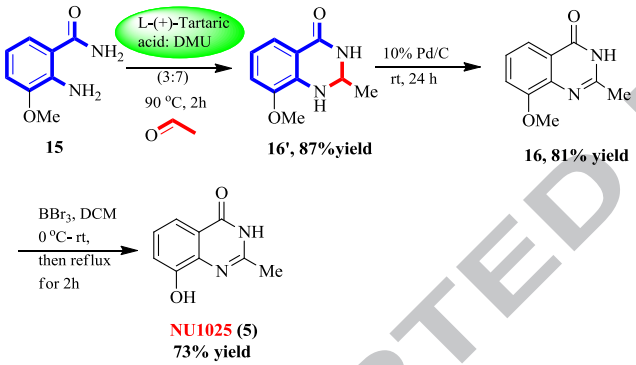


It was further aromatized to 2-(4-(benzyloxy)benzyl)quinazolin-4(3*H*)-one (**12**) in 82% yield using DDQ in dry DCM. The benzylic oxidation of Compound **12** was achieved with KBr/Oxone in DCM-$MeNO_2$ solvent to obtain compound **13** in 73% yields. Next, the deprotection of the benzyl group with H_2 on Pd/C not only deprotected the benzyl group but unfortunately

also reduced the benzylic carbonyl to secondary alcohol (**14, scheme 5**). Hence, that benzylic hydroxy of compound **14** was again oxidised with Pyridinium chlorochromate (PCC) in DCM to obtain penipanoid C (**3**) in 85% yield. 2-(4-Hydroxybenzyl)quinazolin-4(3*H*)-one (**4**) was also obtained *via* debenzylation of compound **12** with hydrogen in Pd/C. We have accomplished the first total syntheses of penipanoid C and 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one in overall 36.6% and 57% yield respectively.

Further, we were eager to synthesize **NU1025** [8-hydroxyl-2-methyl-4(3*H*)-quinazoline] (**Scheme 4**) using this green deep eutectic solvent mediated cyclization strategy due to its diverse pharmacological properties (*vide supra*). In the beginning, 2-amino-3-methoxybenzamide (**15**) was synthesized from 3-methoxy-2-aminobenzoic acid *via* two steps which on treatment with acetaldehyde solution in low melting mixtures at 90 ^{0}C furnished 8-methoxy-2-methyl-2,3-dihydroquinazolin-4(1*H*)-one (**16'**) in 87% yield in 2h. It was further aromatized to quinazolionone product **16** with 10% Pd/C at rt. Treatment of compound **16** with BBr_3 in dry DCM in reflux condition, deprotected the methoxy group that led to NU1025(**5**) in 73% yield and we have completed the synthesis of NU1025 with 51.4% overall yield.

Scheme 4: Synthesis of 8-hydroxyl-2-methyl-4(3*H*)-quinazoline (**NU1025**)



In conclusion, we have utilized a milder and economical strategy for the synthesis of dihydroquinazolinones to synthesize naturally occurring alkaloids penipanoid C and 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one have synthesized for the first time with overall good yields. NU1025 drug also been synthesized using this DES protocol.

Acknowledgments

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Supplementary Material

NMR, CHN, LCMS and HRMS spectra are available in supporting information

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Highlights:

- The first total synthesis of penipanoid C and 2-(4-hydroxybenzyl)quinazolin-4(3*H*)-one is reported.
- A greener mild deep eutectic solvent mediated cyclization strategy was used with good overall yields.
- NU1025 drug is also synthesized using the similar protocol.