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Synthesis of Hexahydro-3H-Xantheno [1, 2-C] Isoxazole by Using Novel Methodology and Evolution of Anticancer Activity

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ABSTRACT

A different isoxazolidine and isoxazoline derivatives have been prepared through a dipolar cycloaddition of olefinic band carbaldehyde with hydroxylamines. This is the methodology for the preparation of highly diastereoselective isoxazolidine derivatives from alkene contains chromene-3-carboxaldehyde. This method is operationally simple and works with a diverse range of substrates and some of the prepared isoxazoles exhibits anticancer activity.

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INTRODUCTION:

Isooxazoles are five-membered nitrogen-containing heterocycles frequently present in various biologically active molecules.[1] They are found to show a wide spectrum of pharmacological activities.[2] Notably, chromeno[4,3-*c*]isoxazolines possess anti-depressant, anti-cancer, and ant-anxiolytic behavior (Figure 1).[3] Due to the labile nature of the N-O bond, isoxazolidines act as a rich source of 1,3-amino alcohols.[4]

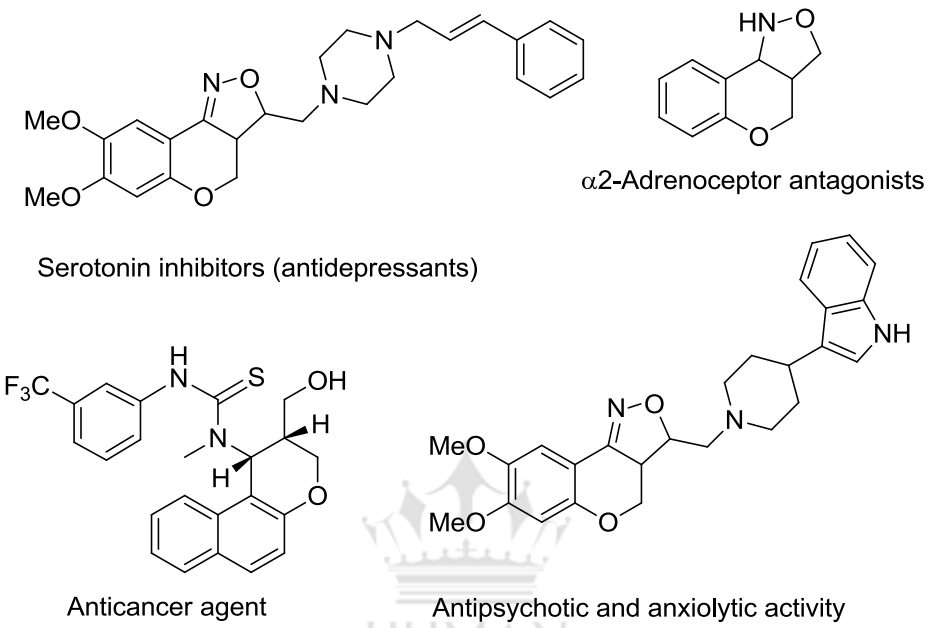
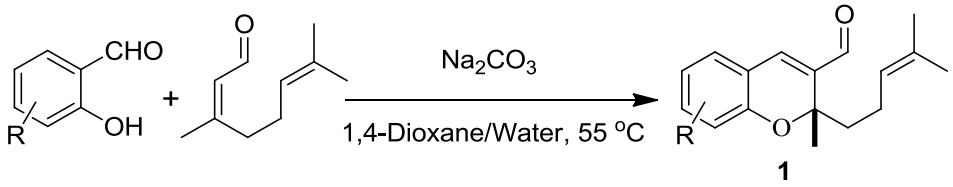


Figure No 1: Biologically active isoxazole derivatives

Of a variety of methods, the 1,3-dipolar cycloaddition of nitrones is one of the shortest methods for the synthesis of these heterocycles.[5] In particular, the intramolecular version of this reaction provides structurally more complex fused isoxazolidine derivatives.[6] Furthermore, chromene skeleton is present in several naturally occurring bioactive molecules.[7] Therefore, it is expected that xantheno[1,2-*c*]isoxazole derivatives may also exhibit significant bioactivity. Furthermore, there has been a new methodology developed on the synthesis of xantheno[1,2-*c*]isoxazoles from alkene-contains chromene-3-carboxaldehyde and hydroxylamine.

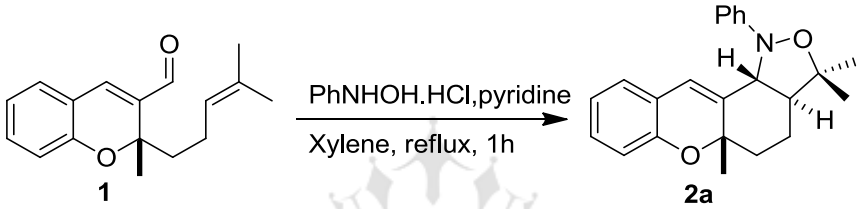
Following our interest in intramolecular cycloaddition reactions,[8]we herein report a novel methodology for the synthesis of tetracyclic xantheno[1,2-*c*]isoxazole derivatives utilizing a [1,3]-dipolar cycloaddition of alkene-contains chromene-3-aldehyde and *N*-substituted

hydroxylamine. The required alkene- contains chromene-3-aldehyde was prepared in 60% yield from citral and 2-hydroxybenzaldehyde in the presence of a base (Scheme 1).[9]



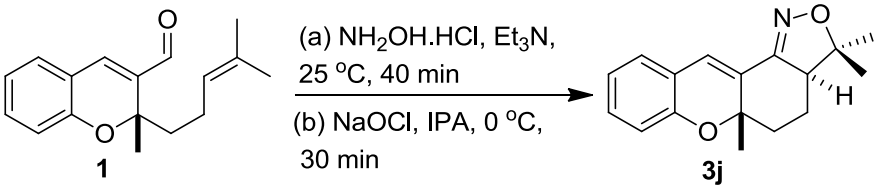
Scheme No. 1: Preparation of chromene-3-carboxaldehyde(**1**)

Our preliminary experiment was carried out between alkene-appended chromene-3-aldehyde (**1**) and *N*-phenylhydroxylamine. hydrochloride (**2**) in the presence of pyridine in Xylene. The reaction proceeded under refluxing conditions resulted in the formation of isoxazolidine**3a** in 85% yield (Scheme 2).



Scheme No. 2: Synthesis ofisoxazolidine**2a**

These initial findings expectant us to investigate the scope of this reaction. Interestingly, the reaction proceeded well with chromene-3-carboxaldehyde bearing chloro and bromo substituents on the aromatic ring (Table 1). The reaction was successful not only with *N*-phenyl but also with *N*-methyl and *N*-benzyl derivatives (entries a-i, Table 1). Next, we extended this method to simple hydroxylamine hydrochloride. Notably, the corresponding isoxazoline derivative **3j** was obtained in 80% yield (Scheme 3, entry j, Table 1).



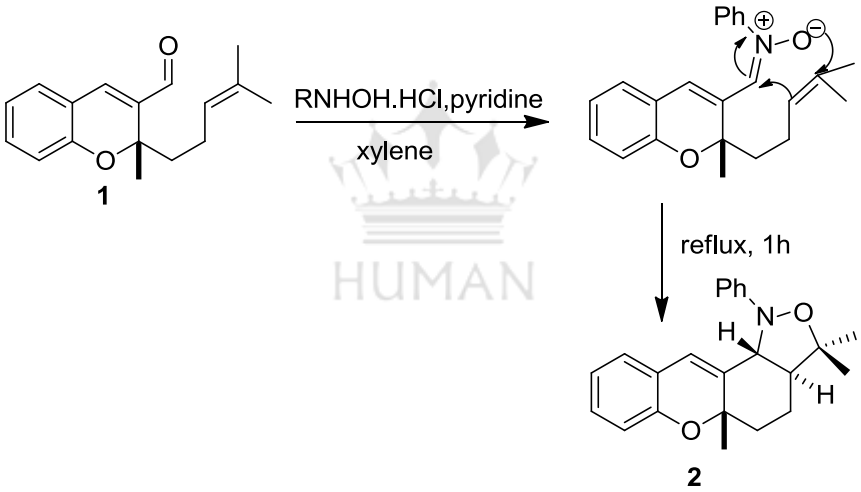
Scheme No. 3: Synthesis ofisoxazoline**3j**

The above reaction proceeds in two steps. In the first step, the oxime is formed from the aldehyde and hydroxylamine in the presence of triethylamine. In the second step, the nitrile

oxide is formed by the reaction of oxime with NaOCl. Subsequently, the nitrile oxide undergoes an intramolecular cycloaddition with internal olefin would give the desired isoxazoline 3.[10]similarly, halo substituted chromene-3-carboxaldehyde was also found to be equally effective for this transformation (entries k & l, Table 1). All the products were thoroughly characterized by NMR, IR, and mass spectrometry. The structure and relative of 3l were further confirmed by a single crystal X-ray crystallography.

In all cases, the reactions are highly diastereoselective affording the desired products in good yields. In the case of **2**, a single diastereomer was formed in each reaction, which was confirmed by the NMR spectrum of the unpurified sample.

Mechanistically, the reaction is expected to proceed via the nitrone formation from chromene-3-aldehyde and hydroxylamine. A subsequent 1,3-dipolar cycloaddition of nitrone with internal olefin would result in the formation of isoxazolidine**2** (Scheme 4).



Scheme No. 4: A plausible reaction pathway

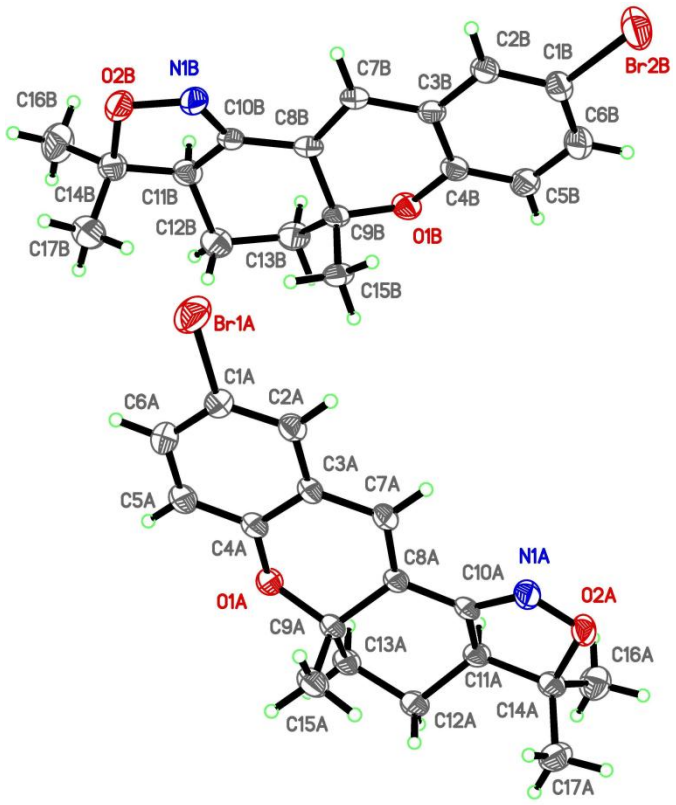
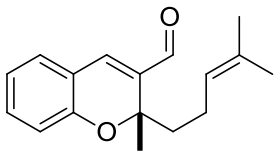
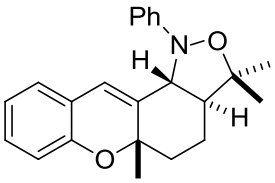
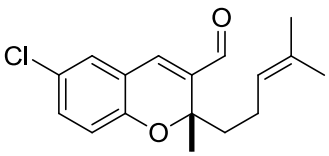
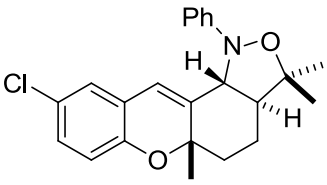
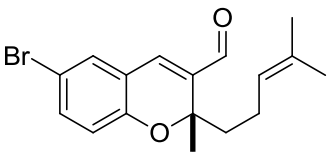
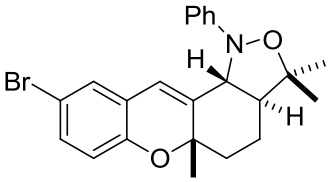
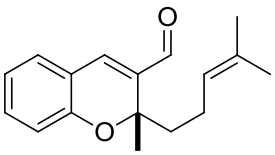
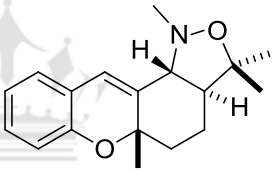
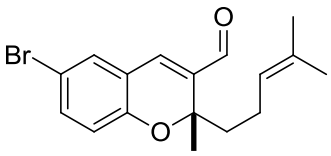
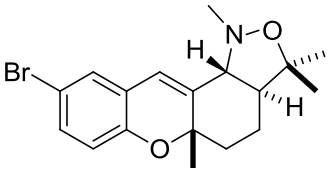
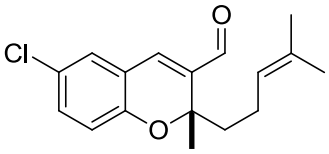
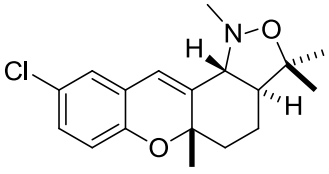
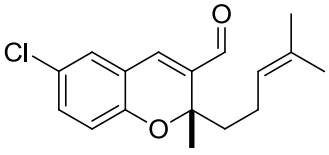
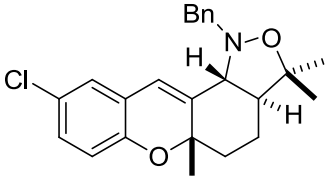
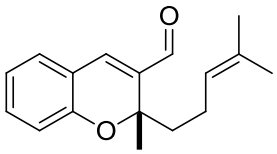
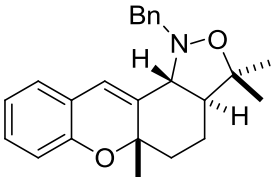
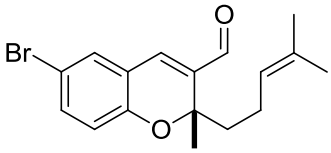
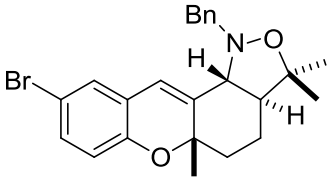
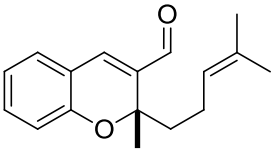
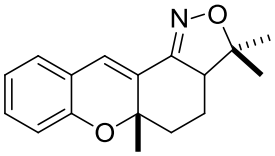
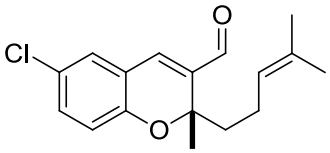
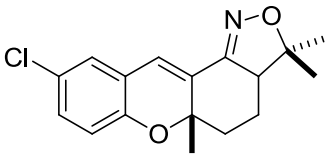
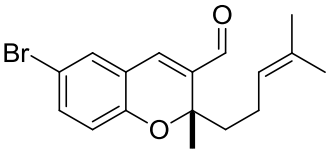
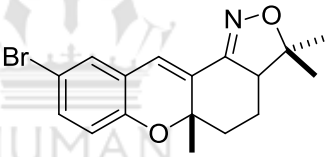


Figure No. 2: ORTEP diagram of **3l**

Table 1

Entry	Substrate (**1**)	Product (**2/3**)[a]		Yield (%)[b]
a			**2a**	85
b			**2b**	81
c			**2c**	83
d			**2d**	90
e			**2e**	87
f			**2f**	85
g			**2g**	90

h			**2h**	85
i			**2i**	87
j			**3a**	80
k			**3b**	78
l			**3c**	81

[a]All products were characterized by NMR, IR and mass spectroscopy.
[b]Isolated yield after purification

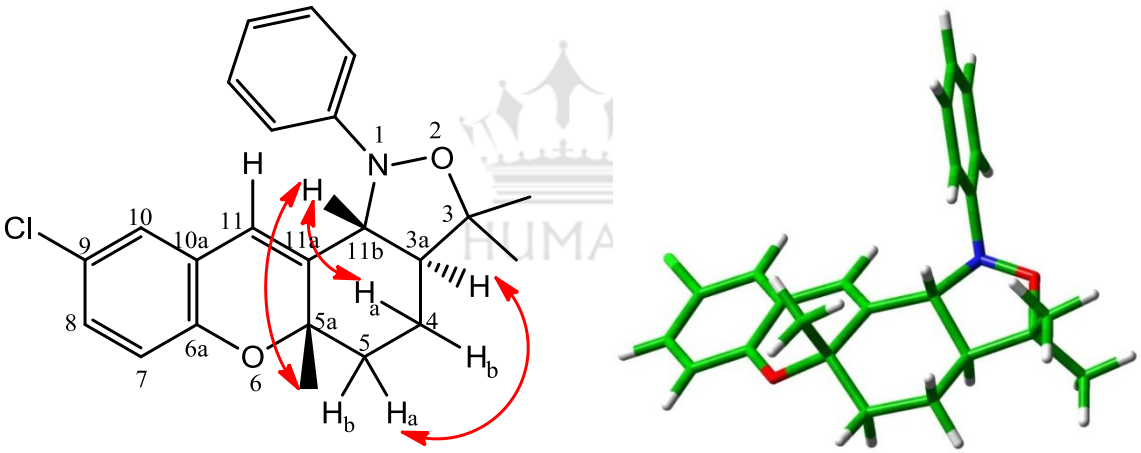
In conclusion, we have demonstrated an efficient synthesis of polycyclic isoxazolidine derivatives from alkene appended chromene-3-carboxaldehyde and substituted hydroxylamines using 1,3-dipolar nitrone cycloaddition. This method also provides isoxazoline derivatives from the corresponding aldehyde and hydroxylamine hydrochloride.

NMR Spectral Data:

1D (^{1}H, ^{1}H-^{1}H Homo-nuclear Decoupling, and ^{13}C) and 2D (gDQCOSY, NOESY, TOCSY, and HSQC) NMR spectra of compound-I dissolved in $CDCl_3$, are recorded at 298 K on a Bruker Avance-III 500 MHz (^{13}C at 125 MHz) spectrometers Chemical shifts (δ) are reported in ppm and tetramethylsilane (TMS) δ=0.00 ppm for ^{1}H ($CDCl_3$ δ=77.00 ppm for ^{13}C) is used as the internal standard. Coupling constants (*J*) are reported in hertz (Hz). The following

abbreviations are used to designate the multiplicities: d=doublet, dd= doublet of the doublet, and m=multiplet.

The structure of compound-I is confirmed by the incisive NMR studies such as 2D-NOESY, and *J*-coupling analysis. From the one dimensional ^{1}H NMR data, the observed strong scalar coupling constants, $^{3}J_{3(a)\text{-}H/11(b)\text{-}H}$ = 11.3, $^{3}J_{3(a)\text{-}H/4\text{-}H(a)}$ = 10.6, and $^{3}J_{4\text{-}H(a)/5\text{-}H(a)}$ = 10.8 clearly indicate that the 3(a)H, 4H(a), 5H(a) and 11(b)H protons are in axial position in the six-membered ring. 4H(b), and 5H(b) and their corresponding scalar coupling values $^{3}J_{4\text{-}H(b)/3(a)\text{-}H}$ = 5.1, $^{3}J_{4\text{-}H(b)/5\text{-}H(a)}$ = 6.4, and $^{3}J_{4\text{-}H(b)/5\text{-}H(b)}$ = 3.2 Hz, respectively have suggested that 4H(b), and 5H(b) protons are in equatorial position in the six-membered ring. The characteristic NOE correlations {3(a)H- 5H(a)}, {4H(a)-11(b)H}, and {5(a)CH_3-11(b)H}, along with scalar coupling constant analysis have confirmed that the six-membered ring is in chair conformation. The energy minimized structure of compound-I adequately supports our NMR analysis (Figure 1).



Cytotoxicity:

To study the possible pharmacological activity, some of the selected xantheno [1, 2-c] isoxazole homologous were subjected to *insemination* cytotoxicity to human alveolar epithelial cell line (A549) and mouse macrophage cell (B-16). Cytotoxicity of test compounds in cells was determined by MTT [3-(4, 5-dimethylthaizol-2-yl)-2, 5-diphenyl tetrazolium bromide] assay.

In general, the majority of the tested compounds showed moderate to strong cytotoxicity to the above two cell lines. Among the tested compounds, **2c** showed the most potent cytotoxicity to A549 with an IC50 value of 0.19 lg/mL (Table 1, entry 3) and compound **2f** exhibited the strongest cytotoxicity to the B-16 cell line with an IC50 value of 1.9 lg/mL

(Table 1, entry 6). It is noteworthy that 2H-chromene analog **3f** also showed remarkable cytotoxicity to A549cell line with IC50 value 3.20 lg/mL. It is fascinating that both the compounds **2c** and **2f** (Table 2) may be helpful to increase their cytotoxicity. Therefore, these isoxazole derivatives may become promising antitumor drug candidates for further pharmacological studies to discover efficient chemotherapeutics for the healing of human cancer diseases.

Table 2 Cytotoxicity of novel polycyclic isooxazole analogs **2**

Entry	Compound 3	Cytotoxicity to carcinoma cells $1C_{50}$ [a] (μM)	
		A549	B-16
1	2a	18.76	11.45
2	2b	22.42	12.43
3	2c	**0.19**	8.47
4	2d	9.58	35.7
5	2e	14.02	12.0
6	2f	**3.20**	**1.9**
7	2g	NA	7.69
8	2h	11.36	11.3
9	2i	20.36	12.42
10	3a	11.26	7.32
10	Doxorubicin(control)	<0.1	<0.1

NA = no activity.

[an] IC_{50} value corresponded to the compound concentration causing 50%mortality in carcinoma after 72h incubation. The data is a mean value of three repeated experiments.

CONCLUSION:

In conclusion, we have verified a route for the synthesis of hexahydro-3H-xanthene [1, 2-c] isoxazole by using a novel methodology. Some of these molecules **2c, 2f** are found to possess potent cytotoxicity against two carcinoma cell lines. We believe 3H-xantheno [1, 2-c] isoxazolemay find a medicinal application after structural modulation and further biological studies.

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