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Synthesis of new optically pure isoxazolines via 1,3-dipolar cycloaddition of nitrile oxides with allyl esters derived from eugenol

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ABSTRACT

1,3-dipolar cycloaddition of arylnitrile oxides with allyl ester prepared from eugenol afforded new chiral isoxazolines in good yields. The chemical structure of this compounds was characterized by ^{1}H NMR,^{13}C NMR, 2D NMR and TOF-MS analysis. All the cycloadducts were obtained through a regiospecific and stereospecific pathway and all cases, only one isomer was isolated, as established by unambiguous NMR analysis.

Keywords

1,3-dipolar cycloaddition, arylnitrile oxides, allyl esters, isoxazolines, regiospecific reaction.

Academic Discipline And Sub-Disciplines

Chemistry

SUBJECT CLASSIFICATION

Organic Synthesis

TYPE (METHOD/APPROACH)

1,3-dipolar cycloaddition reactions

INTRODUCTION

Heterocyclic compounds have a wide range of applications in synthetic organic chemistry. Especially, isoxazolines are of considerable interest due to their versatile applications in pharmaceutical and agrochemical fields. Isoxazoline derivatives have been reported to possess anti influenza virus,[1] glycoprotein IIb/IIIa receptor antagonists,[2] antidiabetic,[3] antitumour,[4] antifungal,[5] analgesic, anti-inflammatory,[6] spermicidal and anti HIV,[7] *β*-adrenergic receptor antagonist,[8] antistress[9] and anticancer properties.[10]
In fact, the combrestatine A-4, analogous **1-3** and the Avicine **4** compound derived from isoxazolines possess anti-cancer activities.[11]

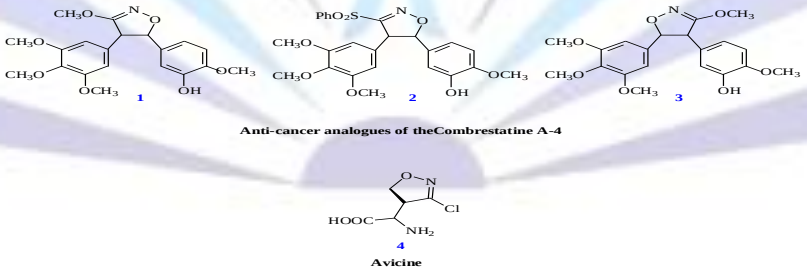

Figure 1- Representative examples of anti-cancer isoxazoline derivatives.

The 1,3-dipolar cycloaddition reactions represent one of the best method for the preparation of five-membered heterocycles,[12] and natural products.[13] In particular the 1,3-dipolar cycloaddition of nitrile oxides with alkenes and alkynes afforded isoxazolines which are used as intermediates for the synthesis of *β*-amino alcohols and alkaloids.[14,15]
In order to increase the activities of the cycloadducts, we have used the eugenol [4-allyl-2methoxyphenol] as a precursseur of the dipolarophiles because it is well known that this natural compound have different biological activities such as antispasmodic,[16] antipyretic,[17] anti-inflammatory,[18] and antibacterial activities.[19]
Herein, we report an efficient and practical procedure for the preparation of new optically pure isoxazolines **7(ad-cf)** via the 1,3-dipolar cycloaddition of the arylnitrile oxides with esters, synthesized from eugenol and having a terminal double bond. The reaction was carried out in toluene at 80 ° C without a catalyst.

Results and discussion

Dipolarophiles **5(a-c)** were prepared in two steps (Scheme1). The first one concern the synthesis of the *N*-protected aminoacids. The condensation of the later compounds with eugenol gave the corresponding esters.[20]

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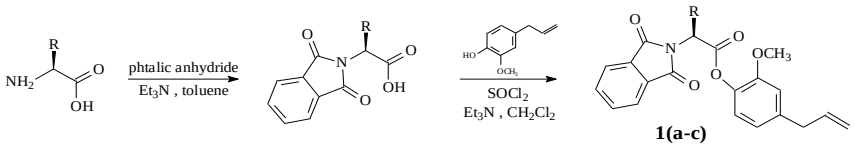
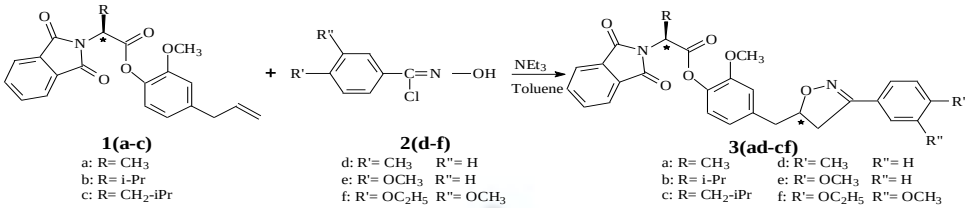


Scheme 1- Synthesis of the optically pure esters derived from eugenol and amino acid.

Arylnitrile oxides were easily generated *in situ* from benzohydroxyaminoyl chlorides **6(d-f)** with triethylamine in toluene according to a known procedure.[21] The cycloaddition reaction of dipolarophiles **5(a-c)** with the arylnitrile oxides at reflux of toluene for 48h (Scheme2) afforded the isoxazolines **7(ad-cf)** with good yields as indicated in table 1.



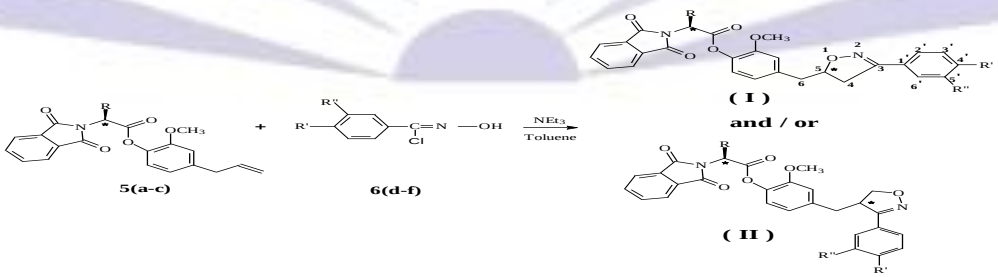
Scheme 2-1,3-Dipolar cycloaddition reaction of benzohydroxyaminoyl chlorides **6(d-f)** with allyl esters **5(a-c).**

Table 1. Yields of cycloadducts **3(ad-cf)**

Entry	R	R'	R"	Cycloadducts	Yields %
1	CH_3	CH_3	H	**3ad**	58%
2	CH_3	OCH_3	H	**3ae**	72%
3	CH_3	OC_2H_5	OCH_3	**3af**	61%
4	i-Pr	CH_3	H	**3bd**	62%
5	i-Pr	OCH_3	H	**3be**	60%
6	i-Pr	OC_2H_5	OCH_3	**3bf**	65%
7	CH_2-i-Pr	CH_3	H	**3cd**	60%
8	CH_2-i-Pr	OCH_3	H	**3ce**	68%
9	CH_2-i-Pr	OC_2H_5	OCH_3	**3cf**	62%

Regiochemistry and stereochemistry of the cycloaddition

Two possible regioisomers **I** and **II** can be theoretically formed (Scheme 3) [22]. In practice, we have obtained only one product as evidenced by TLC and ^{1}H NMR examination of the crude mixture. Cycloadducts **7(ad-cf)** have been purified by a column chromatography and characterized by NMR (^{1}H and ^{13}C). Based on the literature [23] and the ^{13}C NMR, we can conclude that the new cycloadducts possess the same stereochemistry as detailed below. The cycloaddition of the amino esters **7(ad-cf)** with the arylnitrile oxides led to new cycloadducts having a new chiral center: the quaternary carbon linked to the substituted phenyl group of the isoxazoline ring.



Scheme 3- Regiochemistry of cycloaddition.

Compound **7cd** was obtained as a yellow liquid. Its positive ES–MS showed a pseudo-molecular ion peak $[M+H]^+$ at m/z = 541 compatible with the molecular formula $C_{32}H_{32}N_2O_6$. The structure was confirmed by the disappearance in the ^{1}HNMR spectrum of the signal at δ_H 5.01 ppm relative to the terminal ethylenic protons and the appearance of a doublet of doubets signal at δ_H 2.98(dd, 1H$_{4'}$, J_1= 7.8 Hz, J_2= 16.5 Hz) and 3.25(dd, 1H$_{4''}$, J_1= 10.2 Hz, J_2= 16.8 Hz) attribuable to the proton H_4 and the presence of a singlet at δ_H 2.33 (s, 3H) corresponding to the methyl protons. A characteristic AA'BB' pattern for aromatic hydrogens was observed in the ^{1} H NMR spectrum. Examination at 300 MHz offered an excellent resolution with a doublet at δ_H 7.14 (d, 2H, J = 8.1 Hz, H$_{3',5'}$) and a second doublet at δ_H 7.48 (d, 2H, J = 8.1 Hz, H$_{2',6'}$). The ^{13}C NMR spectrum confirmed the above spectral data by the observation of signals at 126.0 (C$_{1'}$), 126.2 (C$_{2',6'}$), 128.8 (C$_{3',5'}$) and 139.7 (C$_{4'}$) ppm relative to the carbons of the *p*-substituted aromatic system. The same spectrum

showed signals at δ_C 80.9 and 155.9 atributable to the bearing oxygen carbon C_5 and C_3 of imine fonction, respectively. In addition, a whole set of linkages confirming the molecular structure of compound **7cd** was reinforced by the HMBC spectrum which showed correlations between the proton H_4 and $C_{1'}$, C_3 , C_5 and C_6 as well as correlations between $H_{2',6'}$ and $C_{1'}$, C_3 and $C_{4'}$. Moreover the regiochemistry was confirmed by the NOE observed between the protons H_4 and the aromatic protons $H_{2',6'}$. Although in this study the novel isoxazoline derivatives **7(ad-cf)** were formed as an unique products indicating the regiospecificity of the reaction. Indeed the non-formation of the other 1,5-regioisomer may be explained by a possible steric crowding and by electronic factors.

Experimental section

Solvents were purified by standard methods. Melting points were determined on a Buchi SMP-20 capilary apparatus and are uncorrected. TLC was carried out on a Merck 60F-254 precoated silica gel plates (0.25 mm) and column chromatography was performed with Merck silica gel (70-230 mesh). NMR spectra were recorded on a Bruker AC-300 spectrometer (^{1}H NMR at 300 MHz and ^{13}C NMR at 75.5 MHz) with $CDCl_3$ as solvent and TMS as internal standard reference. Et_3N was purchased from Acros. All starting protected amino esters were prepared according to the procedure.[21] In all cases, the crude amino esters was purified before use.[24] The benzohydroxyaminoyl chlorides **6(d-f)** were prepared according to the literature procedures.[22]

General procedure for the preparation of the new isoxazolines

A magnetically stirred solution of amino esters (**5a-c**) and the appropriate precursor of the benzohydroxyaminoyl chlorides in dry toluene, was refluxed under nitrogen for 15 min. Et_3N (2 mL) was then added and the mixture was stirred and refluxed for 48 h. After the filtration of the triethylamine hydrochloride, the solvent was evaporated and the residue was purified by silica gel column chromatography (eluent: cyclohexane-AcOEt, 70:30).[25]

2-methoxy-4-{[3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methyl}phenyl2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanoate(7ae)

Yellow liquid (72%). ***^{1}H NMR*** (300MHz, $CDCl_3$): $\delta = 1.72$(d, 3H, -CH3, J = 7.2Hz), 2.81-2.88(dd, 1H, J_1= 6.9 Hz, J_2= 14.1 Hz), 3.00-3.36 (m, 3H), 3.76(s,3H, -OCH_3), 3.79(s,3H, -OCH_3), 4.95-4.99(m, 2H), 6.74(d, 1H, aromatic, J = 7.4 Hz), 6.87(d, 1H,aromatic, J = 7.8 Hz), 7.19-7.22(m, 2H, aromatics), 7.30(s, 1H, aromatic), 7.53-7.56(m, 2H, aromatics), 7.74-7.76(m, 2H, aromatics), 7.87-7.90(m, 2H, aromatics),. ***^{13}C NMR*** (75.5MHz, $CDCl_3$): $\delta = 20.9(CH_3)$, 38.9(CH_2), 40.1(CH_2), 50.8(OOC-CH-N), 55.3(OCH_3), 55.4(OCH_3), 81.3(CH-O), 111.4($CH_{aromatic}$), 113.8($2CH_{aromatic}$), 121.5($CH_{aromatic}$), 123.0($CH_{aromatic}$), 126.0($C_{aromatic}$), 127.6($C_{aromatic}$), 128.6($2CH_{aromatic}$), 129.0($2CH_{aromatic}$), 131.4($C_{aromatic}$), 133.8($2CH_{aromatic}$), 137.7($C_{aromatic}$), 139.9($C_{aromatic}$), 151.2($C_{aromatic}$), 156.0(C=N), 167.4(N-C=O), 170.8(COO). TOFMS ES $^+$ for $C_{29}H_{26}N_2O_7$ theoretical $[M+H]^+$: 515.1740; measured $[M+H]^+$: 514.1743

2-methoxy-4-{[3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methyl}phenyl2-(1,3 dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate (7be)

Yellow liquid (60%). ***^{1}H NMR*** (300MHz, $CDCl_3$): $\delta = 1.01$(d, 3H, -CH3, J = 6.6Hz), 1.25(d, 3H, -CH3, J = 6.6 Hz), 2.33-2.38(m, 2H), 2.97-3.29(m,4H), 3.73(s,3H, -OCH_3), 3.75(s,3H, -OCH_3), 4.87-4.90(m, 1H), 6.81-6.86(m, 2H, aromatics), 6.99-7.02(dd, 1H,aromatic, J_1= 1.5 Hz, J_2= 8.1 Hz), 7.19-7.21(m, 2H, aromatics), 7.52-7.55(m, 2H, aromatics), 7.75-7.58(m, 2H, aromatics), 7.91-7.94(m, 2H, aromatics). ***^{13}C NMR*** (75MHz, $CDCl_3$): $\delta =$ 20.3(CH_3), 20.9(CH_3), 28.0(CH), 38.9(CH_2), 40.1(CH_2), 50.1(OOC-CH-N), 55.2(OCH_3), 55.4(OCH_3), 81.0(CH-O), 111.4($CH_{aromatic}$), 113.0($2CH_{aromatic}$), 122.2($CH_{aromatic}$), 123.0($CH_{aromatic}$), 126.0($C_{aromatic}$), 128.6($C_{aromatic}$), 129.0($2CH_{aromatic}$), 129.3($2CH_{aromatic}$),131.3($C_{aromatic}$), 133.7($2CH_{aromatic}$), 137.8($C_{aromatic}$), 139.8($C_{aromatic}$), 150.4($C_{aromatic}$), 156.0(C=N), 167.2(N-C=O), 171.4(COO). TOFMS ES $^+$ for $C_{31}H_{30}N_2O_7$ theoretical $[M+H]^+$: 525.2053; measured $[M+H]^+$: 525.2057

2-methoxy-4-{[3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methyl}phenyl 2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-methylpentanoate (7ce)

Yellow liquid (68%). ***^{1}H NMR*** (300MHz, $CDCl_3$): $\delta = 0.99$(d, 3H, -CH3, J = 6.6Hz), 1.03(d, 3H, -CH3, J = 6.6 Hz), 1.59-1.62(m,1H), 2.06-2.17(m, 2H), 2.97-3.36(m,4H), 3.79(s,3H, -OCH_3), 3.89(s,3H, -OCH_3), 4.93-4.98(m, 1H), 5.23-5.29(dd, 1H, J_1= 4.2 Hz, J_2= 11.4 Hz), 6.72-6.88(m, 2H, aromatics), 6.99-7.02(dd, 1H,aromatic, J_1= 1.5 Hz, J_2= 8.1 Hz), 7.19(s, 1H), 7.74-7.78(m, 3H, aromatics), 7.86-7.92(m, 2H, aromatics), 7.97-8.00(m, 2H, aromatics). ***^{13}C NMR*** (75.5MHz, $CDCl_3$): $\delta =$ 20.9(CH_3), 21.2(CH_3), 22.7(CH), 38.9(CH_2), 39.0(CH_2), 40.3(CH_2), 50.0(OOC-CH-N), 55.4(OCH_3), 55.6(OCH_3), 81.0(CH-O), 111.4($CH_{aromatic}$), 113.8($2CH_{aromatic}$), 121.5($CH_{aromatic}$), 123.0($CH_{aromatic}$), 126.0($C_{aromatic}$), 126.2($C_{aromatic}$), 128.9($2CH_{aromatic}$), 129.0($2CH_{aromatic}$),129.7($C_{aromatic}$), 133.7($2CH_{aromatic}$), 137.8($C_{aromatic}$), 139.8($C_{aromatic}$), 150.4($C_{aromatic}$), 156.0(C=N), 167.2(N-C=O), 170.8(COO). TOFMS ES $^+$ for $C_{32}H_{32}N_2O_7$ theoretical $[M+H]^+$: 557.2209; measured $[M+H]^+$: 557.2205.

2-methoxy-4-{[3-(4-methylphenyl)-4,5-dihydroisoxazol-5-yl]methyl}phenyl 2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanoate (7ad)

Yellow liquid (58%). ***^{1}H NMR*** (300MHz, $CDCl_3$): $\delta = 1.86$(d, 3H,-CH_3, J= 7.2 Hz), 2.39(s, 3H, -CH_3), 2.84-2.91(dd, 1H, J_1= 6.9 Hz, J_2= 14.1 Hz), 2.99-3.07(dd, 1H, J_1= 7.8 Hz, J_2= 16.5 Hz), 3.12-3.18(dd, 1H, J_1= 6.3 Hz, J_2= 13.8 Hz), 3.28-3.36(dd, 1H, J_1= 8.1 Hz, J_2= 17.2 Hz), 3.82(s, 3H, -OCH_3), 4.93-4.99(m, 1H), 5.30(q, 1H, J= 9.9 Hz), 6.81-6.84(dd, 1H, J_1= 1.5 Hz, J_2= 8.1 Hz), 6.89(s,1H, aromatic), 7.02-7.05(dd, 1H, J_1= 1.5 Hz, J_2= 8.1 Hz), 7.21(d, 2H, aromatics, J= 8.1 Hz), 7.55(d,2H, aromatics, J= 8.1 Hz), 7.75-7.79(m,2H, aromatics),7.89-7.94(m, 2H, aromatics).***^{13}C NMR*** (75.5MHz, $CDCl_3$): $\delta =$ 14.8(CH_3), 20.9(CH_3), 39.0(CH_2), 40.4(CH_2), 46.9(OOC-CH-N), 55.4(OCH_3), 80.9(CH-O-N), 113.1($CH_{aromatic}$), 113.1($CH_{aromatic}$), 119.5($CH_{aromatic}$), 123.0($2CH_{aromatic}$), 126.0($C_{aromatic}$), 126.2($CH_{aromatic}$), 128.8($2CH_{aromatic}$), 128.8($C_{aromatic}$), 131.5($CH_{aromatic}$), 133.6($C_{aromatic}$), 135.7($C_{aromatic}$), 136.1($C_{aromatic}$), 150.4($C_{aromatic}$), 155.9(C=O), 166.8(N-C=O), 167.5(COO). TOFMS ES $^+$ for $C_{29}H_{26}N_2O_6$ theoretical $[M+H]^+$: 499.1790; measured $[M+H]^+$: 499.1788.

2-methoxy-4-{[3-(4-methylphenyl)-4,5-dihydroisoxazol-5-yl]methyl}phenyl 2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate (7bd)

Yellow liquid (62%). ***[1]H NMR*** (300MHz, $CDCl_3$): δ =0.95(d, 3H_e, -CH_3, J= 7.3 Hz), 1.14-1.17(m, 4H), 2.27(s,3H,-CH_3), 2.76-3.29(m, 4H), 3.63(s, 3H, -OCH_3), 4.76-4.79(m, 2H), 6.68-6.76(m, 2H, aromatics), 6.89-6.92(dd, 1H, aromatic, J_1= 3.00 Hz, J_2= 8.1 Hz), 7.09(d, 2H, aromatics, *J*= 8.1 Hz), 7.43(d, 2H, aromatics, *J*= 8.1 Hz), 7.65-7.68(m, 2H, aromatics), 7.80-7.82(m, 2H, aromatics).***[13]C NMR*** (75.5MHz, $CDCl_3$): δ = 18.8(CH_3), 20.2(CH_3), 20.9(CH_3), 28.0(CH), 39.0(CH_2), 40.3(CH_2), 55.2(OCH_3), 57.0(OOOC-CH-N), 81.0(CH-O-N), 113.0($CH_{aromatic}$), 119.5($CH_{aromatic}$), 120.8($CH_{aromatic}$), 122.2(2$CH_{aromatic}$), 123.0($C_{aromatic}$), 125.0(2$CH_{aromatic}$), 126.0($C_{aromatic}$), 126.2(2$CH_{aromatic}$), 128.8($C_{aromatic}$), 131.7($C_{aromatic}$), 133.7($C_{aromatic}$), 135.7($C_{aromatic}$), 150.4($C_{aromatic}$), 155.9(C=N), 166.4(N-C=O), 167.1(COO). TOFMS ES $^+$ for $C_{31}H_{30}N_2O_6$ theoretical $[M+H]^+$: 527.2103; measured $[M+H]^+$: 527.2105

2-methoxy-4-{[3-(4-methylphenyl)-4,5-dihydroisoxazol-5-yl]methyl}phenyl 2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-4-methylpentanoate (7cd)

Yellow liquid (60%). ***[1]H NMR*** (300MHz, $CDCl_3$): δ = 0.95(d, 3H, -CH3, *J* = 6.6Hz), 0.98(d, 3H, -CH3, *J* = 6.3Hz), 1.53-1.59(m,1H), 2.04-2.13(m, 1H), 2.33(s,3H,-CH_3), 2.39-2.50(m, 1H), 2.79-2.84(dd, 1H, J_1= 6.6Hz, J_2= 13.8 Hz), 2.92-3.00(dd, 1H, J_1= 7.8 Hz, J_2= 16.5 Hz), 3.04-3.11(dd, 1H, J_1= 6.3Hz, J_2= 13.8 Hz), 3.21-3.30(dd, 1H, J_1= 10.2 Hz, J_2= 16.8 Hz), 3.74(s,3H, -OCH_3), 4.86-4.92(m, 1H), 5.18-5.23(dd, 1H, J_1= 4.5 Hz, J_2= 11.1 Hz), 6.75(d, 1H, *J* = 7.8 Hz), 6.82(s, 1H), 6.94-6.97(dd, 1H, J_1= 0.9 Hz, J_2= 7.8 Hz), 7.14(d, 2H, aromatics, *J* = 8.1 Hz), 7.48(d, 2H, aromatics, *J* = 8.1 Hz), 7.69-7.72(m, 2H, aromatics), 7.82-7.86(m, 2H, aromatics). ***[13]C NMR*** (75MHz, $CDCl_3$): δ = 20.65, 20.90, 22.67, 24.64, 36.82, 39.08, 40.38, 50.12, 55.44, 80.99, 113.12, 120.80, 122.09, 123.01, 126.07, 126.29, 128.88, 131.41, 133.67, 135.78, 137.96, 139.76, 150.45, 155.96, 167.14, 167.62. TOFMS ES $^+$ for $C_{32}H_{32}N_2O_6$ theoretical $[M+H]^+$: 541.2349; measured $[M+H]^+$: 541.2346.

4-{[3-(4-ethoxy-3-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methyl}-2-methoxyphenyl 2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanoate (7af)

Yellow liquid (61%). ***[1]H NMR*** (300MHz, $CDCl_3$): δ =1.41(t, 3H, -CH_3, *J*= 7.2 Hz), 1.79(d, 3H, -CH3, *J*= 7.2 Hz), 2.76-2.83(dd, 1H, J_1= 6.9 Hz, J_2= 13.8 Hz), 2.90-2.98(dd, 1H, J_1= 8.1 Hz, J_2= 16.8 Hz), 3.02-3.09(dd, 1H, J_1= 6.3 Hz, J_2= 14.1 Hz), 3.19-3.28(dd, 1H, J_1= 9.9 Hz, J_2= 16.5 Hz), 3.74(s, 3H,-OCH_3), 3.83(s, 3H, -OCH_3), 4.06(q, 2H, -OCH_2, *J*= 7.2 Hz), 4.84-4.90(m, 1H), 5.22(q, 1H, *J*= 7.5 Hz), 6.74-6.79(m, 2H, aromatics), 6.83(s, 1H, aromatic), 6.90-6.985(m, 2H, aromatics), 7.29(d,1H, *J*= 1.5 Hz), 7.66-7.71(m, 2H, aromatics), 7.81-7.84(m, 2H, aromatics).***[13]C NMR*** (75.5MHz, $CDCl_3$): δ = 14.1(CH_3), 14.8(CH_3), 39.0(CH_2), 40.3(CH_2), 46.9(OOC-CH-N), 55.4(OCH_3), 55.3(OCH_3), 63.7(O-CH_2), 80.9(CH-O), 108.4($CH_{aromatic}$), 111.2($CH_{aromatic}$), 113.1($CH_{aromatic}$), 119.71($CH_{aromatic}$), 120.8($CH_{aromatic}$), 121.7($C_{aromatic}$), 122.0($C_{aromatic}$), 122.9(2$CH_{aromatic}$), 131.4($CH_{aromatic}$), 133.6(2$CH_{aromatic}$), 135.8($C_{aromatic}$), 137.9($C_{aromatic}$), 148.8($C_{aromatic}$), 149.6($C_{aromatic}$), 150.4($C_{aromatic}$), 155.7(C=N), 166.7(N-C=O), 167.5(COO). TOFMS ES $^+$ for $C_{31}H_{30}N_2O_8$ theoretical $[M+H]^+$: 559.2002; measured $[M+H]^+$: 559.2006.

4-{[3-(4-ethoxy-3-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methyl}-2-methoxyphenyl 2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-methylbutanoate (7bf)

Yellow liquid (65%). ***[1]H NMR*** (300MHz, $CDCl_3$): δ =0.96 (d, 3H, *J*= 6.6 Hz), 1.19 (d, 3H, -CH_3, *J*= 6.6Hz), 1.42 (t, 3H, -CH_3, *J*= 6.9 Hz), 2.77-3.09(m, 4H), 3.19-3.28(dd, 1H, J_1= 10.2 Hz, J_2= 16.5 Hz), 3.23(s,3H, -OCH_3), 3.67(s,3H, -OCH_3), 4.07(q, 2H,-OCH_2-, *J*= 7.2 Hz), 4.81-4.87(m, 2H), 6.73-6.77(m, 2H, aromatics), 6.80(d, 1H_{16}, aromatic, J= 4.2 Hz), 6.92-6.97(m, 2H, aromatics), 7.30(d,1H, *J*= 1.5Hz), 7.69-7.73(m, 2H, aromatics), 7.82-7.87(m, 2H, aromatique); ***[13]C NMR*** (75.5MHz, $CDCl_3$): δ = 14.6(CH_3), 19.3(CH_3), 20.7(CH_3), 28.4(CH), 39.5(CH_2), 40.8(CH_2), 55.7(OCH_3), 55.9(OCH_3), 57.5(OOC-CH-N), 64.3(OCH_2), 81.5(CH-O), 108.95($CH_{aromatic}$), 111.8($CH_{aromatic}$), 113.5($CH_{aromatic}$), 120.2($C_{aromatic}$), 121.2($CH_{aromatic}$), 121.3($C_{aromatic}$), 122.7($CH_{aromatic}$), 123.5($CH_{aromatic}$), 131.7($CH_{aromatic}$), 134.2($CH_{aromatic}$), 136.2($C_{aromatic}$), 138.2($C_{aromatic}$), 149.3($C_{aromatic}$), 150.1($C_{aromatic}$), 150.9($C_{aromatic}$), 156.2(C=N), 166.9(N-C=O), 167.6(COO). TOFMS ES $^+$ for $C_{33}H_{34}N_2O_8$ theoretical $[M+H]^+$: 587.2315; measured $[M+H]^+$: 587.2314.

4-{[3-(4-ethoxy-3-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methyl}-2-methoxyphenyl 2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-methylpentanoate (7cf)

Yellow liquid (62%). ***[1]H NMR*** (300MHz, $CDCl_3$): δ =0.97(d, 3H, -CH_3, *J*= 6.6 Hz), 1.00 (d, 3H, -CH_3, *J*= 6.3Hz), 1.45 (t, 3H, -CH_3, *J*= 7.2 Hz), 1.58(m,1H), 2.03-2.47(m, 2H), 2.78-2.85(dd, 1H, J_1= 6.9 Hz, J_2= 14.1 Hz), 2.93-3.01(dd, 1H, J_1= 7.8 Hz, J_2= 16.5 Hz), 3.07-3.14(dd,1H, J_1= 6.3 Hz, J_2= 13.8 Hz), 3.23-3.28(dd, 1H, J_1= 8.1 Hz, J_2= 16.5 Hz), 3.77(s,3H, -OCH_3), 3.87(s,3H, -OCH_3), 4.10(q, 2H,-OCH_2, *J*= 6.9 Hz), 4.88-4.94(m, 1H), 5.20-5.25(dd, 1H, J_1= 4.5 Hz, J_2= 11.1 Hz), 6.76-6.99(m, 5H, aromatics), 7.33(d,1H, *J*= 1.8Hz), 7.71-7.75(m, 2H, aromatics), 7.85-7.88(m, 2H, aromatics); ***[13]C NMR*** (75.5MHz, $CDCl_3$): δ = 14.6(CH_3), 21.1(CH_3), 25.1(CH_3), 26.9(CH), 39.5(CH_2), 40.6(CH), 40.8(CH_2), 50.6(OOC-C-N), 55.9(2 OCH_3), 64.3(O-CH_2), 81.5(CH-O), 108.9($CH_{aromatic}$), 111.7($CH_{aromatic}$), 113.6($CH_{aromatic}$), 120.2($CH_{aromatic}$), 121.2($CH_{aromatic}$), 121.3($CH_{aromatic}$), 122.2($C_{aromatic}$), 122.5($C_{aromatic}$), 123.5($CH_{aromatic}$), 129.0($C_{aromatic}$), 131.8($CH_{aromatic}$), 134.1($C_{aromatic}$), 136.2($C_{aromatic}$), 138.4($C_{aromatic}$), 149.3($C_{aromatic}$)150.1($C_{aromatic}$), 156.2(C=N), 167.6(N-C=O), 168.12(COO). TOFMS ES $^+$ for $C_{34}H_{36}N_2O_8$ theoretical $[M+H]^+$: 601.2471; measured $[M+H]^+$: 601.2467.

Conclusion

We have studied the reactivity of allyl esters **5(a–c)** toward acyclic benzohydroxyaminoyl chlorides **6(d-f)**. All cycloadducts were formed in appreciable regiospecificity and chemospecificity, giving the products in good yields. The continuous pharmaceutical interest in the isoxazoline compounds may justify further exploration of these results in the pharmacological field.

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Figures captions

Figure 1- Representative examples of anti-cancer isoxazoline derivatives.
Scheme 1- Synthesis of the optically pure esters derived from eugenol and amino acid.
Scheme 2-1,3-Dipolar cycloaddition reaction of benzohydroxyaminoyl chlorides **6(d-f)** with allyl esters **5(a-c).**
Scheme 3- Regiochemistry of cycloaddition.