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From 4,5,6,7-tetrahydroindoles to 3- or 5-(4,5,6,7-tetrahydroindol-2-yl)isoxazoles in two steps: a regioselective switch between 3- and 5-isomers

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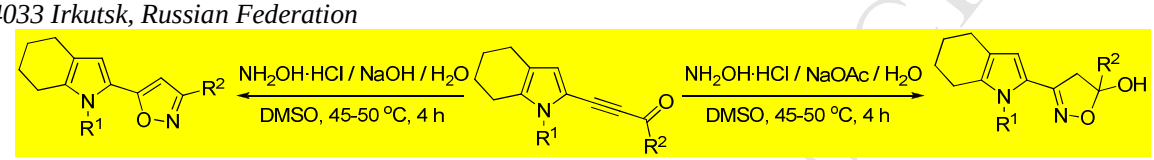

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>From 4,5,6,7-tetrahydroindoles to 3- or 5-(4,5,6,7-tetrahydroindol-2-yl)isoxazoles in two steps: a regioselective switch between 3- and 5-isomers

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isoxazoles

ABSTRACT

(4,5,6,7-Tetrahydroindol-2-yl)alkynes, synthesized by cross-coupling of 4,5,6,7-tetrahydroindoles with aroyl(hetaroyl)bromoalkynes or ethyl bromopropynoate in the presence of K_2CO_3, regioselectively cyclize with hydroxylamine to either 3- or 5-(4,5,6,7-tetrahydroindol-2-yl)isoxazoles depending on the acidity of the reaction mixture: in the presence of acetic acid 3-isomers are formed (*ca.* 100% selectivity), while under neutral conditions the reaction is switched to 5-isomers (94-97% selectivity).

1. Introduction

Isoxazoles and their derivatives are important scaffolds for the synthesis of various natural compounds and their congeners.[1] The interest in isoxazoles is steadily growing as they are potent, selective agonists for human cloned dopamine D4 receptors,[2] $GABA_A$ receptor antagonist,[3] COX-2,[4] tyrosine kinase[5] and HIV-1 replication[6] inhibitors, exhibit analgesic,[7] antiinflammatory,[5] anticancer,[8] antimicrobial[9] (including antitubercular[10]), antifungal,[11] antiviral,[12] antipsychotic,[13] and hypoglycemic[14] activities. Many known drugs (sulfisoxazoles,[15] antibiotics: oxacillin, cloxacillin and dicloxacillin,[16] isocarboxazide, a monoaminoxidase inhibitor used in psychotherapy,[17] and agarin, which acts on the central nervous system[18]) contain isoxazole rings. Fused isoxazoles are present in the structure of anabolic steroids[15] and compounds possessing antimetastatic activity.[19]

The high potential of isoxazoles as protecting functions and their tendency to be converted into other functionalities ensure their wide spread use in organic synthesis.[1]

As important areas of isoxazole application intensify, the search for shorter and simpler routes to their novel derivatives, including their ensembles with other heterocycles, particularly with pyrrole or indole rings increases. The latter may additionally improve pharmaceutically targeted properties of these ensembles. This is supported for instance by the fact that pyrrolyl- and indolylisoxazoles are selective inhibitors of protein kinase C,[20] used as fatty acid amide hydrolase inhibitors,[21] and agonists of α7 nicotinic acetylcholine receptors,[22] have anticancer,[23] antimicrobial[24] and anti-inflammatory[25] activities.

Among the known methods of isoxazole synthesis, [2+3]-cycloaddition of 1,3-dipoles to alkynes and the reaction of hydroxylamine with 1,3-diketone or an α,β-unsaturated ketones are the most important.[26] Although frequently used, majority of the above routes lead to mixtures of regioisomers.[26,27] However, in some cases, the reactions can be directed to selective formation of a single isomer by changing either the process conditions or the substrate structure. For example, ethynyl ketones bearing amino acid moieties react with hydroxylamine in the presence of pyridine to form a mixture of regioisomers,[27] while without pyridine, selective oximation of the carbonyl group with following cyclization occurs.[27] On the contrary, for the selective oximation of the carbonyl group in diphenylpropynones, pyridine is required, whereas other isomer is formed with sodium carbonate.[28] Gemdifluoroethynyl ketones give with hydroxylamine both the expected isomers of isoxazoles, with or without pyridine.[29]

In spite of that, the control of regioselectivity of the isoxazole synthesis remains a challenge for organic chemistry.

A few known regioselective syntheses of isoxazoles comprise of the addition of hydroxylamine to α-benzotriazolyl-α,β-unsaturated ketones[30] and β-dimethylaminovinyl ketones,[31] the

reactions of chalcones with hydroxylamine hydrochloride using K_2CO_3 as solid support under microwave conditions,[32] cyclization of α,β-unsaturated aldehydes/ketones with *N*-hydroxyl-4-toluenesulfonamide,[33] a ruthenium (II)-,[34] or copper(I)-[35] catalyzed cycloaddition reaction between nitrile oxides and acetylenes, and also four-component interaction of a terminal alkyne, hydroxylamine, carbon monoxide, and an aryl iodide in the presence of a palladium catalyst.[36]

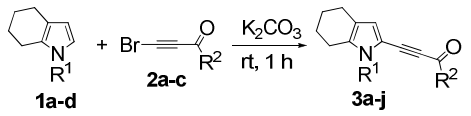
2. Result and discussion

Here we report an efficient regioselective synthesis of (4,5,6,7-tetrahydroindol-2-yl)isoxazoles that allows the preparation of either 3- or 5-isomers from the same starting materials depending on media acidity.

The method consists of the cyclization of (4,5,6,7-tetrahydroindol-2-yl)alkynes **3a-j** with hydroxylamine. The former have been synthesized by cross-coupling of 4,5,6,7-tetrahydroindoles **1a-d** with aroyl(hetaroyl)bromoalkynes **2a-c** (Table 1) or ethyl bromopropynoate in the presence of K_2CO_3 [37]

Table 1

The cross-coupling of 4,5,6,7-tetrahydroindoles **1a-d** with aroyl(hetaroyl)bromoalkynes **2a-c**



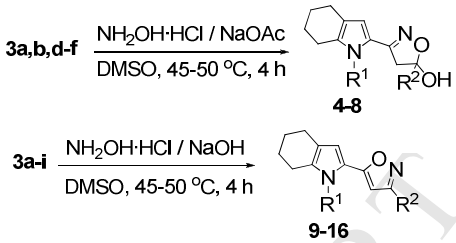
1a-d **2a-c** **3a-j**

Ethynylpyrrole **3**	Yield, %	Ethynylpyrrole **3**	Yield, %
3a	54[37]	**3f**	52
3b	68[37]	**3g**	44
3c	71[37]	**3h**	48
3d	70[37]	**3i**	67
3e	43	**3j**	41

3-(4,5,6,7-Tetrahydroindol-2-yl)-2-propynones **3a-i** readily cyclize with hydroxylamine (10-fold excess) to give regioselectively either 3-(4,5,6,7-tetrahydroindol-2-yl)-4,5-dihydroisoxazol-5-ols **4-8** or 5-(4,5,6,7-tetrahydroindol-2-yl)isoxazoles **9-16** (Table 2). The cyclization can be easily switched from the direction leading exclusively to isoxazoles **4-8** to the formation of isoxazoles **9-16** by simple changing of the proton concentration in the reaction mixture. When the reaction is carried out in the presence of acetic acid ($NH_2OH·HCl$/NaOAc, 1:1 system), only isoxazoles **4-8** are formed, whereas under neutral or basic conditions ($NH_2OH·HCl$/NaOH (1:1 or 1:1.5 system), the cyclization takes another pathway to produce preferably (94-97% or entirely) isoxazoles **9-16**.

Table 2

Cyclocondensation of 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynones **3a-i** with NH_2OH

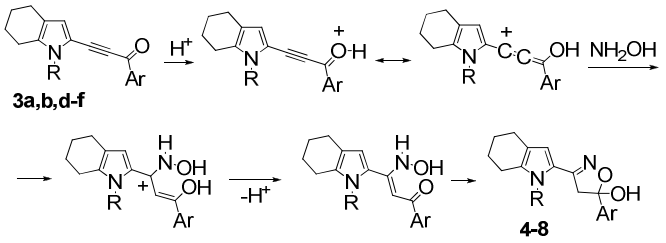


Isoxazoles **4-16**	Yield, %	Isoxazoles **4-16**	Yield, %
4	85	**11**	91
5	90	**12**	91
6	90	**13**	88
7	80	**14**	76 (^{1}H NMR)
8	87	**15**	80
9	85	**16**	90
10	86		

Noteworthy, with the excess NaOH (in the system $NH_2OH·HCl$/NaOH, 1:1.5 molar ratio), 4,5-dihydroisoxazol-5-ols are not detected in the reaction mixture at all.

Apparently, in the presence of acetic acid, the attack of the NH_2OH nucleophile at the β-acethylenic carbon of ketones **3a,b,d-f** is electrophilically assisted by the simultaneous protonation of the carbonyl group (and finally 1,4-addition takes place to deliver isoxazoles **4-8**), (Scheme 1).

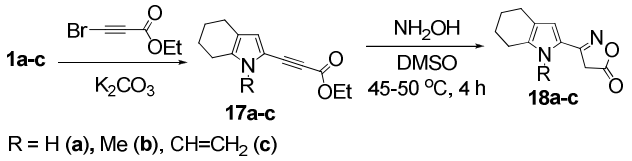
Scheme 1.



The switch to the formation of isoxazoles **9-16** occurs when the system $NH_2OH·HCl/NaOAc$ is replaced by the $NH_2OH·HCl/NaOH$ system, which is unable to exert the electrophilic assistance and hence the common oximation of the carbonyl group prevails. Interestingly, some other ethynyl ketones react with hydroxylamine hydrochloride in the presence of KOH to selectively yield 4,5-dihydroisoxazol-5-ols, i.e. the reaction proceeds across the triple bond.[38]

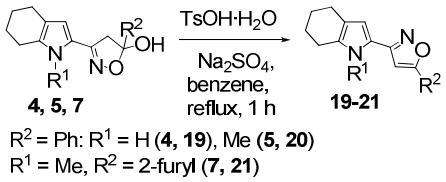
In the case of 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates **17a-c**, easily available from 4,5,6,7-tetrahydroindoles **1a-c** and ethyl bromopropynoate,[39] the cyclization with hydroxylamine results in isoxazolinones **18a-c** only (Scheme 2, Table 3).

Scheme 2.



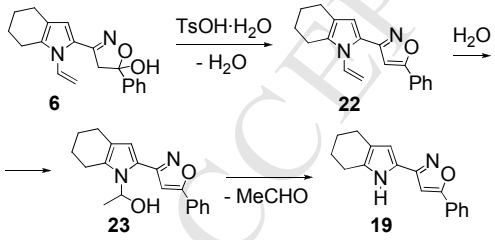
4,5-Dihydroisoxazol-5-ols **4, 5, 7** undergo easy aromatization when refluxing (benzene, 1 h) in the presence of $TsOH·H_2O$ to isoxazoles **19-21** in 73-92% yield (Scheme 3).

Scheme 3.



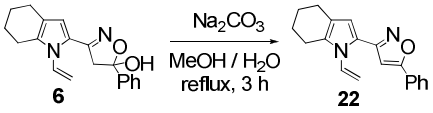
Under the same conditions dehydration of *N*-vinylisoxazole **6** is accompanied by devinylation to afford *N*H-isoxazole **19** in 58% yield (Scheme 4). Apparently this is a result of the electrophilic addition of water to the vinyl group of isoxazole **22** and subsequently decomposition of the hemiaminal **23** (Scheme 4).

Scheme 4.



N-Vinyl-derivative **6** has been dehydrated with retention of *N*-vinyl group (Scheme 5) in boiling aqueous methanol in the presence of Na_2CO_3 according to the published procedure.[40]

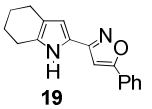
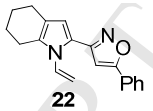
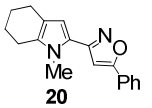
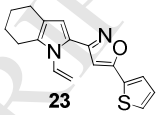
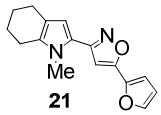
Scheme 5.



In some cases (e.g., with R^2 = 2-thienyl) the aromatization of 4,5-dihydroisoxazol-5-ol occurs during the synthesis (compound **23**, Table 3).

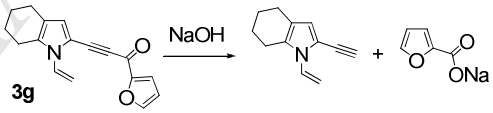
Table 3.

The isoxazoles **19-23**, synthesized by dehydration of 3-(4,5,6,7-tetrahydroindol-2-yl)-4,5-dihydroisoxazol-5-ols

Isoxazoles **8**	Yield, %	Isoxazoles **8**	Yield, %
 **19**	89	 **22**	49
 **20**	91	 **23**	79
 **21**	73		

The cyclization of propynone **3g** in the presence of $NH_2OH·HCl/NaOH$ is accompanied by the cleavage (under the action of hydroxide ion) of the acyl-acetylene bond to give terminal acetylene (Scheme 6) that agrees with earlier reports.[41]

Scheme 6.



3. Conclusion

In conclusion, we have developed regioselective route to functionalized tetrahydroindole-isoxazole ensembles using nucleophilic addition of hydroxylamine to the triple bond or the carbonyl group of (4,5,6,7-tetrahydroindol-2-yl)alkynes, the products of cross-coupling of 4,5,6,7-tetrahydroindoles with aroyl(hetaroyl)bromoalkynes or ethyl bromopropynoate in the presence of K_2CO_3 The synthesized compounds represent a new family of promising precursors for the drug design, potent building blocks for heterocyclic synthesis.

4. Experimental section

4.1. General information

IR spectra were obtained on a Bruker IFS-25 spectrometer (400-4000 cm^{-1}, KBr pellets or thin films). ^1H (400.13 MHz), ^{13}C (100.61 MHz) NMR spectra were recorded on a Bruker Avance 400 instrument in $CDCl_3$. The assignment of signals in the ^1H NMR spectra was made using COSY and NOESY experiments. Resonance signals of carbon atoms were assigned based on ^1H-^{13}C HSQC and ^1H-^{13}C HMBC experiments. The ^1H and ^{13}C chemical shifts were referenced to HMDS. The chemical shifts were recorded in ppm.

1-Phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynone **3a** was prepared according to the procedure reported.[42] 1-Phenyl-3-(1-methyl- (**3b**) and 1-phenyl-3-(1-benzyl-(**3c**)-4,5,6,7-

tetrahydro-1*H*-indol-2-yl)-2-propynones were prepared according to the published procedure[43] and 1-phenyl-3-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynone **3d** was prepared according to the literature procedure.[44]

4.2. General procedure of 1-hetaryl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynones 3e-j preparation

Equimolar amounts (0.5-1.0 mmol) of 4,5,6,7-tetrahydroindole **1b-d** and hetaroylbromoalkyne **2b,c** were ground at room temperature with a 10-fold amount (by weight) of K_2CO_3 in a china mortar for 10 min. The reaction mixture self-heated (5-8°C) and within 10 min turned from yellow to orange-brown. After 60 min the reaction mixture was placed on the column with Al_2O_3 and eluted with *n*-hexane to afford pure 1-hetaryl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynone **3e-j**.

*4.2.1. 1-(Furan-2-yl)-3-(1-methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)prop-2-yn-1-one (**3e**).*

Yield 43%; yellow crystals; mp 138 °C; [Found: C, 75.92; H, 5.90; N, 5.39. $C_{16}H_{15}NO_2$ requires C, 75.87; H, 5.97; N, 5.53%]; ν_{max}(KBr) 2170 (C≡C), 1610 (C=O) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.62 (1 H, dd, *J* 1.7, 0.8 Hz, H-5 of furan), 7.27 (1 H, dd, *J* 3.6, 0.8 Hz, H-3 of furan), 6.57 (1 H, s, H-3), 6.55 (1 H, dd, *J* 3.6, 1.7 Hz, H-4 of furan), 3.60 (3 H, s, NMe), 2.55-2.52 (2 H, m, CH_2-7), 2.49-2.46 (2 H, m, CH_2-4), 1.84-1.81 (2 H, m, CH_2-6), 1.72-1.69 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 164.2, 153.1, 146.6, 135.7, 119.5, 118.9, 118.2, 112.0, 110.3, 95.4, 88.7, 30.7, 22.8, 22.5, 22.3. 22.1.

*4.2.2. 3-(1-Benzyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-1-(furan-2-yl)prop-2-yn-1-one (**3f**).*

Yield 52%; yellow crystals, mp 115 °C; [Found: 80.34; H, 5.89; N, 4.24. $C_{22}H_{19}NO_2$ requires C, 80.22; H, 5.81; N, 4.22%]; ν_{max}(KBr) 2163 (C≡C), 1610 (C=O) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.52 (1 H, dd, *J* 1.7, 0.8 Hz, H-5 of furan), 7.34-7.30 (2 H, m, H_m Ph), 7.28-7.26 (1 H, m, H_p Ph), 7.12-7.10 (3 H, m, H_o Ph, H-3 of furan), 6.66 (1 H, s, H-3), 6.47 (1 H, dd, *J* 3.6, 1.7 Hz, H-4 of furan), 5.21 (2 H, s, CH_2), 2.51-2.48 (2 H, m, CH_2-7), 2.45-2.42 (2 H, m, CH_2-4), 1.77-1.73 (2 H, m, CH_2-6), 1.71-1.67 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 164.1, 153.0, 146.6, 136.9, 135.6, 128.4, 127.1, 126.2, 120.0, 119.5, 118.2, 111.9, 110.5, 95.1, 88.5, 47.8, 22.7, 22.5, 22.4, 22.3.

*4.2.3. 1-(Furan-2-yl)-3-(1-vinyl-4,5,6,7-tetrahydro-1H-indol-2-yl)prop-2-yn-1-one (**3g**).*

Yield 44%; yellow crystals, mp 114 °C; [Found: C, 77.11; H, 5.65; N, 5.30. $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28%]; ν_{max}(KBr) 2167 (C≡C), 1642 (NCH=CH_2), 1608 (C=O) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.61 (1 H, dd, *J* 1.7, 0.8 Hz, H-5 of furan), 7.26 (1 H, dd, *J* 3.6, 0.8 Hz, H-3 of furan), 6.98 (1 H, dd, *J* 16.1, 9.1 Hz, Hx), 6.66 (1 H, s, H-3), 6.55 (1 H, dd, *J* 3.6, 1.7 Hz, H-4 of furan), 5.47 (1 H, d, *J* 16.1 Hz, H_B), 5.01 (1 H, d, *J* 9.1 Hz, H_A), 2.66-2.63 (2 H, m, CH_2-7), 2.49-2.46 (2 H, m, CH_2-4), 1.83-1.79 (2 H, m, CH_2-6), 1.74-1.70 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 164.5, 153.3, 147.2, 135.2, 129.8, 122.1, 121.3, 119.1, 112.4, 110.1, 104.7, 95.1, 88.1, 24.0, 22.9, 22.8, 22.7.

*4.2.4. 3-(1-Methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-1-(thiophen-2-yl)prop-2-yn-1-one (**3h**).*

Yield 48%; yellow crystals, mp 140 °C; [Found: C, 71.40; H, 5.57; N, 5.11; S, 11.68%. $C_{16}H_{15}NOS$ requires C, 71.34; H, 5.61; N, 5.20; S, 11.90%]; ν_{max}(KBr) 2163 (C≡C), 1598 (C=O) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.87 (1 H, dd, *J* 3.7, 1.2 Hz, H-5 of thiophene), 7.63 (1 H, dd, *J* 4.9, 1.2 Hz, H-3 of thiophene), 7.14 (1 H, dd, *J* 4.9, 3.7 Hz, H-4 of thiophene), 6.59 (1 H, s, H-3), 3.61 (3 H, s, NMe), 2.56-2.53 (2 H, m, CH_2-7), 2.50-2.47 (2 H, m, CH_2-4), 1.85-1.80 (2 H, m, CH_2-6), 1.74-1.70 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 168.7, 144.9, 135.6, 133.4, 132.9, 127.7, 119.5, 119.0, 110.3, 95.5, 88.2, 30.8, 22.8, 22.5, 22.3, 22.1.

*4.2.5. 3-(1-Benzyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-1-(thiophen-2-yl)prop-2-yn-1-one (**3i**).*

Yield 67%; yellow crystals, mp 120 °C; [Found: C, 76.60; H, 5.45; N, 4.20; S, 9.19. $C_{22}H_{19}NOS$ requires C, 76.49; H, 5.54; N, 4.05; S, 9.28%]; ν_{max}(KBr) 2157 (C≡C), 1603 (C=O) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.64 (1 H, dd, *J* 3.7, 1.2 Hz, H-5 of thiophene), 7.58 (1 H, dd, *J* 4.9, 1.2 Hz, H-3 of thiophene), 7.32-7.29 (2 H, m, H_m Ph), 7.26-7.23 (1 H, m, H_p Ph), 7.09-7.07 (2 H, m, H_o Ph), 7.03 (1 H, dd, *J* 4.9, 3.7 Hz, H-4 of thiophene), 6.68 (1 H, s, H-3), 5.22 (2 H, s, CH_2), 2.52-2.49 (2 H, m, CH_2-7), 2.45-2.42 (2 H, m, CH_2-4), 1.77-1.75 (2 H, m, CH_2-6), 1.71-1.69 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 169.1, 145.2, 137.2, 135.9, 133.8, 133.4, 128.8, 128.0, 127.5, 126.5, 120.4, 119.9, 110.9, 95.5, 88.3, 48.2, 23.1, 22.9, 22.8, 22.7.

*4.2.6. 1-(Thiophen-2-yl)-3-(1-vinyl-4,5,6,7-tetrahydro-1H-indol-2-yl)prop-2-yn-1-one (**3j**).*

Yield 41%; yellow crystals, mp 97 °C; [Found: C, 72.41; H, 5.41; N, 4.86; S, 11.36. $C_{17}H_{15}NOS$ requires C, 72.57; H, 5.37; N, 4.98; S, 11.40%]; ν_{max}(KBr) 2164 (C≡C), 1645 (N-CH=CH_2), 1593 (C=O) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.87 (1 H, dd, *J* 3.7, 1.2 Hz, H-5 of thiophene), 7.65 (1 H, dd, *J* 4.9, 1.2 Hz, H-3 of thiophene), 7.14 (1 H, dd, *J* 4.9, 3.7 Hz, H-4 of thiophene), 6.99 (1 H, dd, *J* 16.0, 9.0 Hz, H_X), 6.68 (1 H, s, H-3), 5.44 (1 H, d, *J* 16.0 Hz, H_B), 5.04 (1 H, d, *J* 9.0 Hz, H_A), 2.67-2.65 (2 H, m, CH_2-7), 2.51-2.48 (2 H, m, CH_2-4), 1.84-1.80 (2 H, m, CH_2-6), 1.75-1.71 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 169.2, 145.2, 135.1, 134.1, 133.7, 129.8, 128.1, 122.1, 121.3, 110.2, 105.1, 95.2, 87.6, 24.0, 22.9, 22.8, 22.7.

4.3. Synthesis of 5-aryl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-4,5-dihydroisoxazol-5-ols 4-8 (general procedure)

A solution of $NH_2OH{\cdot}HCl$ (2.088 g, 30 mmol) in H_2O (5 mL) was added to a solution of $NaOAc{\cdot}3H_2O$ (4.082 g, 30 mmol) in H_2O (5 mL). The resulting solution was added to a solution of 1-aryl(hetaryl)-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynone **3a,b,d-f** (2.95 mmol) in DMSO (50 mL) and the reaction mixture was stirred at 45-50°C for 4 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with diethyl ether (5 x 30 mL). Ether extracts were washed with water and dried over Na_2SO_4. The residue, after removing solvent, was fractionated by column chromatography (Al_2O_3, *n*-hexane : diethyl ether, 4 : 1) to afford target the 5-aryl-3-(4,5,6,7-tetrahydroindol-2-yl)-5-aryl-4,5-dihydroisoxazol-5-ol **4-8** as yellow, very viscous oil, which transforms to a yellow powder on keeping. In the case of 1-(thiophen-2-yl)-3-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-yn-1-one (**3j**) the product of the reaction is 2-(5-(thiophen-2-yl)isoxazol-3-yl)-1-vinyl-4,5,6,7-tetrahydro-1*H*-indole (**23**).

*4.3.1. 5-Phenyl-3-(4,5,6,7-tetrahydro-1H-indol-2-yl)-4,5-dihydroisoxazol-5-ol (**4**).*

Yield 85%; yellow very viscous oil; [Found: C, 72.06; H, 6.51; N, 9.90. $C_{17}H_{18}N_2O_2$ requires C, 72.32; H, 6.43; N, 9.92%]; ν_{max}(KBr) 3444 (OH), 3249 (NH), 1608 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 8.81 (1 H, br s, NH), 7.62-7.60 (2 H, m, H*o* Ph), 7.39-7.34 (3 H, m, H*m,p* Ph), 6.11 (1 H, s, H-3), 3.53 (1 H, d, *J* 16.9 Hz, CH_2 of isoxazole), 3.39 (1 H, d, *J* 16.9 Hz, CH_2 of isoxazole), 2.97 (1 H, br s, OH), 2.60-2.57 (2 H, m, CH_2-7), 2.47-2.45 (2 H, m, CH_2-4), 1.80-1.78 (2 H, m, CH_2-5), 1.73-1.72 (2 H, m, CH_2-6); δ_C (400 MHz, $CDCl_3$) 151.1, 140.7, 132.7, 128.5,

128.3, 125.7, 118.8, 118.6, 124.5, 106.8, 49.4, 23.5, 23.0, 22.8, 22.6.

*4.3.2. 3-(1-Methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-5-phenyl-4,5-dihydroisoxazol-5-ol (**5**).*

Yield 90%; yellow very viscous oil; [Found: C, 72.86; H, 6.96; N, 9.23. $C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.80; N, 9.45%]; ν_{max}(KBr) 3432 (OH), 1595 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.64-7.62 (2 H, m, H*o* Ph), 7.40-7.34 (3 H, m, H*m,p* Ph), 6.11 (1 H, s, H-3), 3.79 (3 H, s, NMe), 3.58 (1 H, d, *J* 16.9 Hz, CH_2 of isoxazole), 3.46 (1 H, d, *J* 16.9 Hz, CH_2 of isoxazole), 2.97 (1 H, br s, OH), 2.56-2.53 (2 H, m, CH_2-7), 2.48-2.45 (2 H, m, CH_2-4), 1.86-1.80 (2 H, m, CH_2-5), 1.73-1.68 (2 H, m, CH_2-6); δ_C (100.6 MHz, $CDCl_3$) 152.0, 140.9, 134.9, 128.7, 128.5, 125.8, 120.4, 118.3, 113.0, 105.5, 51.2, 33.2, 23.5, 23.1, 23.0, 22.2.

*4.3.3. 5-Phenyl-3-(1-vinyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-4,5-dihydroisoxazol-5-ol (**6**).*

Yield 90%; yellow very viscous oil; [Found: C 73.86; H, 6.60; N, 9.18. $C_{19}H_{20}N_2O_2$ requires C, 74.00; H, 6.54; N, 9.08%]; ν_{max}(KBr) 3414 (OH), 1642 (N-CH=CH_2), 1595 (C=N) cm^{-1}. δ_H (400.13 MHz, $CDCl_3$) 7.63-7.61 (2 H, m, H*o* Ph), 7.53 (1 H, dd, *J* 16.0, 9.0 Hz, H_X), 7.38-7.36 (3 H, m, H*m,p* Ph), 6.18 (1 H, s, H-3), 5.09 (1 H, d, *J* 16.0 Hz, H_B), 5.05 (1 H, d, *J* 9.0 Hz, H_A), 3.58 (1 H, d, *J* 16.8 Hz, CH_2 of isoxazole), 3.45 (1 H, d, *J* 16.8 Hz, CH_2 of isoxazole), 2.99 (1 H, br s, OH), 2.70-2.68 (2 H, m, CH_2-7), 2.50-2.47 (2 H, m, CH_2-4), 1.81-1.77 (2 H, m, CH_2-5), 1.75-1.70 (2 H, m, CH_2-6); δ_C (100.6 MHz, $CDCl_3$) 151.5, 140.6, 134.1, 133.1, 128.6, 128.4, 125.6, 120.5, 120.3, 114.6, 105.6, 105.5, 51.0, 24.8, 23.4, 23.3, 22.8.

*4.3.4. 5-(Furan-2-yl)-3-(1-methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-4,5-dihydroisoxazol-5-ol (**7**).*

Yield 80%, yellow crystals, mp 97 °C; [Found: C, 67.30; H, 6.39; N, 9.66. $C_{16}H_{18}N_2O_3$ requires C, 67.12; H, 6.34; N, 9.78%]; ν_{max}(KBr) 3393 (OH), 1595 (C=N) cm^{-1}. δ_H (400.13 MHz, $CDCl_3$) 7.42-7.41 (1 H, m, H-5 of furan), 6.53-6.52 (1 H, m, H-3 of furan), 6.37-6.36 (1 H, m, H-4 of furan), 6.15 (1 H, s, H-3), 3.75 (3 H, s, NMe), 3.72 (1 H, d, *J* 16.8 Hz, CH_2 of isoxazole), 3.50 (1 H, d, *J* 16.8 Hz, CH_2 of isoxazole), 3.40 (1 H, br s, OH), 2.56-2.53 (2 H, m, CH_2-7), 2.49-2.46 (2 H, m, CH_2-4), 1.86-1.80 (2 H, m, CH_2-5), 1.73-1.68 (2 H, m, CH_2-6); δ_C (100.6 MHz, $CDCl_3$) 152.3, 151.9, 143.7, 135.6, 120.7, 119.0, 113.7, 111.1, 108.6, 102.1, 48.8, 33.7, 24.0, 23.6, 23.5, 22.8.

*4.3.5. 3-(1-Benzyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-5-(furan-2-yl)-4,5-dihydroisoxazol-5-ol (**8**).*

Yield 87%; yellow crystals, mp 114-116 °C; [Found: C, 73.03; H, 6.19; N, 13.39. $C_{22}H_{22}N_2O_3$ requires C, 72.91; H, 6.12; N, 13.24%]; ν_{max}(KBr) 3376 (OH), 1596 (C=N) cm^{-1}. δ_H (400.13 MHz, $CDCl_3$) 7.42-7.41 (1 H, m, H-5 of furan), 7.26-7.24 (2 H, m, H*m* Ph), 7.21-7.17 (1 H, m, H*p* Ph), 7.00-6.98 (2 H, m, H*o* Ph), 6.50-6.49 (1 H, m, H-3 of furan), 6.37-6.36 (1 H, m, H-4 of furan), 6.23 (1 H, s, H-3), 5.57 (1 H, d, *J* 16.4 Hz, CH_2Ph), 5.52 (1 H, d, *J* 16.4 Hz, CH_2Ph), 3.75 (1 H, d, *J* 16.9 Hz, CH_2 of isoxazole), 3.63 (1 H, d, *J* 16.9 Hz, CH_2 of isoxazole), 3.23 (1 H, br s, OH), 2.53-2.50 (2 H, m, CH_2-7), 2.46-2.43 (2 H, m, CH_2-4), 1.79-1.74 (2 H, m, CH_2-5), 1.73-1.69 (2 H, m, CH_2-6); δ_C (100.6 MHz, $CDCl_3$) 151.5, 151.3, 143.2, 138.6, 135.6, 128.6, 127.0, 126.5, 120.3, 119.1, 113.9, 110.7, 108.1, 101.6, 49.1, 48.4, 23.5, 23.2, 23.1, 22.3.

*4.3.6. 2-(5-(Thiophen-2-yl)isoxazol-3-yl)-1-vinyl-4,5,6,7-tetrahydro-1H-indole (**23**).*

Yield 79%; light yellow solid, mp 97 °C; [Found: C, 69.05; H, 5.41; N, 9.22; S, 11.06. $C_{17}H_{16}N_2OS$ requires: C, 68.89; H, 5.44; N, 9.45; S, 10.82%]; ν_{max}(KBr) 1612 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.50-7.49 (1 H, m, H-5 of thiophene), 7.43-7.41 (1 H, m, H-3 of thiophene), 7.40 (1 H, dd, *J* 16.0, 9.0 Hz, H_X), 7.11-7.09 (1 H, m, H-4 of thiophene), 6.47 (1 H, s, H-3), 6.42 (1 H, s, H of isoxazole), 5.08 (1 H, d, *J* 16.0 Hz, H_B), 5.02 (1 H, d, *J* 9.0 Hz, H_A), 2.72-2.69 (2 H, m, CH_2-7), 2.55-2.52 (2 H, m, CH_2-4), 1.84-1.78 (2 H, m, CH_2-6), 1.77-1.73 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 163.7, 156.9, 132.6, 132.5, 129.3, 128.0, 127.8, 126.9, 120.4, 120.3, 112.5, 105.7, 98.6, 24.7, 22.6, 23.1, 23.0.

4.4. Synthesis of 3-aryl(hetaryl)-5-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)isoxazoles 9-16 (general procedure)

A solution of $NH_2OH{\cdot}HCl$ (2.088 g, 30 mmol) in H_2O (5 mL) was added to a solution of NaOH (1.8 g, 45 mmol) in H_2O (5 mL). This was added to a solution of 1-aryl(hetaryl)-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynones **3a-i** (2.95 mmol) in DMSO (50 mL) and the reaction mixture was stirred at 45-50 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with diethyl ether (5 x 30 mL). Ether extracts were washed with water and dried over Na_2SO_4. The residue, after removal of solvent, was crystallized from acetone / H_2O (1:1) to afford target 3-aryl(hetaryl)-5-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)isoxazol **9-16** as light yellow crystals.

*4.4.1. 3-Phenyl-5-(4,5,6,7-tetrahydro-1H-indol-2-yl)isoxazole (**9**).*

Yield 85%; light yellow crystals, mp 146-148 °C; [Found: C 76.89; H, 6.13; N, 10.79. $C_{17}H_{16}N_2O$ requires C, 77.25; H, 6.10; N, 10.60%]; ν_{max}(KBr) 1620 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 8.42 (1 H, br s, NH), 7.82-7.80 (2 H, m, H*o* Ph), 7.44-7.42 (3 H, m, H*m,p* Ph), 6.45 (1 H, d, *J* 2.3 Hz, H-3), 6.43 (1 H, s, H of isoxazole), 2.64-2.61 (2 H, m, CH_2-7), 2.54-2.51 (2 H, m, CH_2-4), 1.86-1.80 (2 H, m, CH_2-6), 1.78-1.73 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 164.5, 162.8, 131.3, 129.9, 129.3, 128.9, 126.9, 119.6, 118.2, 109.2, 93.5, 23.6, 23.1, 22.9, 22.8.

*4.4.2. 5-(1-Methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-3-phenylisoxazole (**10**).*

Yield 86%; light yellow crystals, mp 116-118 °C; [Found: C, 77.67; H, 6.61; N, 9.71. $C_{18}H_{18}N_2O$ requires C, 77.67; H, 6.52; N, 10.06%]; ν_{max}(KBr) 1617 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.83-7.82 (2 H, m, H*o* Ph), 7.45-7.43 (3 H, m, H*m,p* Ph), 6.48 (1 H, s, H-3), 6.45 (1 H, s, H of isoxazole), 3.71 (3 H, s, NMe), 2.59-2.56 (2 H, m, CH_2-7), 2.54-2.51 (2H, m, CH_2-4), 1.89-1.83 (2 H, m, CH_2-6), 1.76-1.71 (2 H, m, CH_2-5); δ_H (100.6 MHz, $CDCl_3$) 165.0, 162.4, 133.3, 129.9, 129.4, 128.9, 126.8, 119.8, 118.7, 110.4, 95.7, 32.0, 23.4, 23.1, 23.0, 22.2; MS (relative intensity), m/z: 278 (100) – M^+, 250 (32), 249 (21), 162 (17), 91 (9), 77 (21), 51 (6).

*4.4.3. 5-(1-Benzyl-4,5,6,7-tetrahydro-1H-indol-2-yl)-3-phenylisoxazole (**11**).*

Yield 91%; light yellow crystals, mp 144-146 °C; [Found: C, 80.93; H, 6.30; N, 7.67. $C_{24}H_{22}N_2O$ requires C, 81.33; H, 6.26; N, 7.90%]; ν_{max}(KBr) 1613 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.72-7.71 (2 H, m, H*o* Ph), 7.40-7.39 (3 H, m, H*m,p* Ph), 7.30-7.26 (2 H, m, H*m* CH_2Ph), 7.22-7.19 (1 H, m, H*p* CH_2Ph), 6.99-6.97 (2 H, m, H*o* CH_2Ph), 6.57 (1 H, s, H-3), 6.29 (1 H, s, H of isoxazole), 5.33 (2 H, s, CH_2Ph), 2.58-2.55 (2 H, m, CH_2-4), 2.49-2.47 (2 H, m, CH_2-7), 1.83-1.78 (2 H, m, CH_2-6), 1.76-1.72 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 164.7 (O-C=), 162.3 (C=N), 138.0 (C*i* CH_2Ph), 133.4 (C-5 of pyrrole), 129.7 (C*p* Ph), 129.2 (C*i* Ph), 128.7 (C*m* Ph, C*m* CH_2Ph), 127.2 (C*p* Ph), 126.7 (C*o* Ph), 125.8 (C*o* CH_2Ph), 119.7 (C-2 of pyrrole), 119.2 (C-4 of pyrrole), 111.1 (*J* 170.3 Hz, C-3 of pyrrole), 95.9 (*J* 95.9 Hz, CH

of isoxazole), 48.1 (CH_2Ph), 23.4 (CH_2-5), 23.1 (CH_2-7), 22.9 (CH_2-6), 22.1 (CH_2-4).

*4.4.4. 2-(3-Furan-2-yl)isoxazol-5-yl)-1-methyl-4,5,6,7-tetrahydro-1H-indole (**12**).*

Yield 91%; light yellow crystals, mp 120-122 °C; [Found: C, 71.71; H, 6.35; N, 10.20. $C_{16}H_{16}N_2O_2$ requires C, 71.62; H, 6.01; N, 10.44%]; ν_{max}(KBr) 1622 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.53-7.52 (1 H, m, H-5 of furan), 6.90-6.89 (1 H, m, H-3 of furan), 6.51-6.50 (1 H, m, H-4 of furan), 6.48 (1 H, s, H-3 of pyrrole), 6.40 (1 H, s, H of isoxazole), 3.69 (3 H, s, NMe), 2.57-2.56 (2 H, m, CH_2-7), 2.51-2.50 (2 H, m, CH_2-4), 1.85-1.84 (2 H, m, CH_2-6), 1.73-1.72 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 164.7, 154.9, 144.7, 143.7, 133.5, 119.5, 118.8, 110.7, 110.6, 109.9, 95.1, 32.0, 23.4, 23.1, 23.0, 22.2.

*4.4.5. 1-Benzyl-2-(3-furan-2-yl)isoxazol-5-yl)-4,5,6,7-tetrahydro-1H-indole (**13**).*

Yield 88%; light yellow crystals, mp 144-146 °C; [Found: C, 76.41; H, 6.04; N, 7.92. $C_{22}H_{20}N_2O_2$ requires C, 76.72; H, 5.85; N, 8.13%]; ν_{max}(KBr) 1613 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.48 (1 H, dd, *J* 1.8, 0.7 Hz, H-5 of furan), 7.29-7.25 (2 H, m, H*m* Ph), 7.22-7.18 (1 H, m, H*p* Ph), 6.97-6.95 (2 H, m, H*o* Ph), 6.81 (1 H, d, *J* 3.4, 0.7 Hz, H-3 of furan), 6.57 (1 H, s, H-3 of pyrrole), 6.47 (1 H, dd, *J* 3.4, 1.8 Hz, H-4 of furan), 6.24 (1 H, s, H of isoxazole), 5.31 (2 H, s, CH_2), 2.57-2.54 (2 H, m, CH_2-7), 2.49-2.46 (2 H, m, CH_2-4), 1.81-1.77 (2 H, m, CH_2-6), 1.76-1.70 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 164.3, 154.7, 144.4, 143.5, 137.8, 133.6, 128.7, 127.2, 125.7, 119.4, 119.2, 111.5, 111.3, 109.7, 95.1, 48.0, 23.3, 23.0, 22.9, 22.1.

*4.4.6. 2-(3-(Furan-2-yl)isoxazol-5-yl)-1-vinyl-4,5,6,7-tetrahydro-1H-indole (**14**).*

This compound is isolated as mixture with 2-ethynyl-1-vinyl-4,5,6,7-tetrahydroindole. Yield 76% (^{1}H NMR); δ_H (400 MHz, $CDCl_3$) 7.46 (1 H, dd, *J* 3.6, 1.0 Hz, H-5 of furan), 7.39 (1 H, dd, *J* 5.0, 1.0 Hz, H-3 of furan), 7.10 (1 H, dd, *J* 5.0, 3.6 Hz, H-4 of furan), 7.02 (1 H, dd, *J* 15.9, 8.8 Hz, H_X), 6.54 (1 H, s, H-3 of pyrrole), 6.39 (1 H, s, H of isoxazole), 5.16 (1 H, d, *J* 15.9 Hz, H_B), 5.13 (1 H, d, *J* 8.8 Hz, H_A), 2.67-2.64 (2 H, m, CH_2-7), 2.55-2.52 (2 H, m, CH_2-4), 1.85-1.79 (2 H, m, CH_2-6), 1.77-1.72 (2 H, m, CH_2-5).

*4.4.7. 1-Methyl-2-(3-thiophen-2-yl)isoxazol-5-yl)-4,5,6,7-tetrahydro-1H-indole (**15**).*

Yield 80%; light yellow crystals, mp 74-76 °C; [Found: C, 67.29; H, 6.00; N, 9.69; S, 11.33. $C_{16}H_{16}N_2OS$ requires C, 67.58; H, 5.67; N, 9.85; S, 11.28%]; ν_{max}(KBr) 1616 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.47 (1 H, dd, *J* 3.6, 1.0 Hz, H-5 of thiophene), 7.39 (1 H, dd, *J* 5.0, 1.0 Hz, H-3 of thiophene), 7.10 (1 H, dd, *J* 5.0, 3.6 Hz, H-4 of thiophene), 6.46 (1 H, s, H-3 of pyrrole), 6.37 (1 H, s, H of isoxazole), 3.69 (3 H, s, NMe), 2.59-2.55 (2 H, m, CH_2-7), 2.53-2.50 (2 H, m, CH_2-4), 1.88-1.82 (2 H, m, CH_2-6), 1.76-1.70 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 165.5, 158.1, 134.0, 131.7, 128.1, 127.8, 127.6, 120.0, 119.3, 111.1, 96.1, 32.5, 23.9, 23.6, 23.4, 22.7.

*4.4.8. 1-Benzyl-2-(3-(thiophen-2-yl)isoxazol-5-yl)-4,5,6,7-tetrahydro-1H-indole (**16**).*

Yield 90%; light yellow crystals, mp 112-114 °C; [Found: C, 73.51; H, 5.40; N, 7.80; S, 9.09. $C_{22}H_{20}N_2OS$ requires C, 73.30; H, 5.59; N, 7.77; S, 8.90%]; ν_{max}(KBr) 1612 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.36-7.35 (2 H, m, H-5, H-3 of thiophene), 7.30-7.26 (2 H, m, H*m* Ph), 7.23-7.19 (1 H, m, H*p* Ph), 7.07-7.04 (1 H, m, H-4 of thiophene), 6.98-6.96 (2 H, m, H*o* Ph), 6.56 (1 H, s, H-3 of pyrrole), 6.21 (1 H, s, H of isoxazole), 5.32 (2 H, s, CH_2Ph), 2.58-2.55 (2 H, m, CH_2-7), 2.49-2.46 (2 H, m, CH_2-4), 1.84-1.78 (2 H, m, CH_2-6), 1.76-1.71 (2 H, m, CH_2-5); δ_C (100.6 MHz, $CDCl_3$) 164.6, 157.5, 152.8, 137.9, 133.6, 131.0, 128.8, 127.5, 127.2, 127.1, 125.8, 119.5, 119.3, 111.3, 95.8, 48.1, 23.3, 23.0, 22.9, 22.1.

4.5. Synthesis of 2-(5-arylisoxazol-3-yl)-4,5,6,7-tetrahydro-1*H*-indoles 19-21 (general procedure)

A solution of 3-(4,5,6,7-tetrahydroindol-2-yl)-5-aryl-4,5-dihydroisoxazol-5-ol **4, 5, 7** (1 mmol) in benzene (10 mL) was refluxed in the presence of *p*-TsOH·H_2O (0.009 g, 0.05 mmol) and Na_2SO_4 (0.284 g, 1 mmol) for 1 h. The cooled reaction mixture was poured into diethyl ether (30 mL) and washed twice with solution of $NaHCO_3$, NaCl and finally with H_2O, dried over $MgSO_4$. After removal of solvent, the residue was purified by column chromatography (Al_2O_3, *n*-hexane : diethyl ether, 10:1) to afford 2-(5-arylisoxazol-3-yl)-4,5,6,7-tetrahydro-1*H*-indole **19-21**.

*4.5.1. 2-(5-Phenylisoxazol-3-yl)-4,5,6,7-tetrahydro-1H-indole (**19**).*

Yield 89%; light yellow solid, mp 208-210 °C; [Found: C, 77.11; H, 5.98; N, 10.49. $C_{17}H_{16}N_2O$ requires C, 77.25; H, 6.10; N, 10.60%]; ν_{max}(KBr) 1620 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 8.77 (1 H, br s, NH), 7.79-7.77 (2 H, m, H*o* Ph), 7.47-7.41 (3 H, m, H*m,p* Ph), 6.61 (1 H, s, H of isoxazole), 6.37 (1 H, s, H-3 of pyrrole), 2.64-2.61 (2 H, m, CH_2-7), 2.55-2.52 (2 H, m, CH_2-4), 1.85-1.80 (2 H, m, CH_2-5), 1.79-1.74 (2 H, m, CH_2-6); δ_C (100.6 MHz, DMSO-d_6) δ 169.6, 158.1, 132.1, 131.7, 130.7, 128.4, 126.9, 119.3, 118.9, 110.6, 99.0, 24.8, 24.3, 23.9, 23.7.

*4.5.2. 1-Methyl-2-(5-phenylisoxazol-3-yl)-4,5,6,7-tetrahydro-1H-indole (**20**).*

Yield 91%; light yellow solid, mp 98-100 °C; [Found: C, 77.38; H, 6.36; N, 10.21. $C_{18}H_{18}N_2O$ requires C, 77.67; H, 6.52; N, 10.06%]; ν_{max}(KBr) 1616 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.80-7.78 (2 H, m, H*o* Ph), 7.47-7.41 (3 H, m, H*m,p* Ph), 6.62 (1 H, s, H of isoxazole), 6.38 (1 H, s, H-3 of pyrrole), 3.82 (3 H, s, NMe), 2.59-2.56 (2 H, m, CH_2-7), 2.55-2.52 (2 H, m, CH_2-4), 1.89-1.83 (2 H, m, CH_2-5), 1.76-1.71 (2 H, m, CH_2-6); δ_C (100.6 MHz, $CDCl_3$) 168.1, 157.3, 133.1, 129.9, 128.9, 127.5, 125.8, 120.5, 118.1, 110.4, 98.4, 32.7, 23.4, 23.1, 22.9, 22.2; MS (relative intensity), m/z: 278 (100) – $M^{+\cdot}$, 274 (16), 250 (34), 249 (10), 176 (23), 173 (31), 148 (20), 105 (36), 91 (8), 77 (36), 51 (8).

*4.5.3. 2-(5-(Furan-2-yl)isoxazol-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-indole (**21**).*

Yield 73%; light yellow solid, mp 80 °C; [Found: C, 71.71; H, 6.35; N, 10.04. $C_{16}H_{16}N_2O_2$ requires C, 71.62; H, 6.01; N, 10.44%]; ν_{max}(KBr) 1651 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.52-7.51 (1 H, m, H-5 of furan), 6.88-6.87 (1 H, m, H-3 of furan), 6.54 (1 H, s, H-4 of isoxazole), 6.52-6.51 (1H, m, H-4 of furan), 6.37 (1 H, s, H-3 of pyrrole), 3.80 (3 H, s, NMe), 2.59-2.57 (2 H, m, CH_2-4), 2.54-2.51 (2 H, m, CH_2-7), 1.89-1.83 (2 H, m, CH_2-5), 1.76-1.70 (2 H, m, CH_2-6); δ_C (100.6 MHz, $CDCl_3$) 160.1, 157.1, 144.0, 143.6, 133.4, 120.3, 118.3, 111.9, 110.8, 110.2, 98.3, 32.8, 23.5, 23.2, 23.1, 22.3.

4.6. 2-(5-Phenylisoxazol-3-yl)-1-vinyl-4,5,6,7-tetrahydro-1*H*-indole (22).

A solution of Na_2CO_3 (1.0 g, 9.43 mmol) in H_2O (5 mL) was added to a solution of 3-(1-vinyl-4,5,6,7-tetrahydroindol-2-yl)-5-aryl-4,5-dihydroisoxazol-5-ol **6** (1.151 g, 4.66 mmol) in MeOH (24 mL). The reaction mixture was refluxed for 3 h. The MeOH was evaporated under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was

evaporated under reduced pressure. Column chromatography (SiO_2, *n*-hexane/Et_2O, 10:1) of the residue afforded isoxazole **8c** (0.663 g, 49%) as light yellow solid, mp 102-104 °C; [Found: C, 78.57; H, 6.24; N, 9.55. $C_{19}H_{18}N_2O$ requires C, 78.59; H, 6.25; N, 9.65%]; ν_{max}(KBr) 1615 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.79-7.77 (2 H, m, H*o* Ph), 7.47-7.41 (4 H, m, H*m*,*p* Ph, H_X), 6.62 (1 H, s, H of isoxazole), 6.45 (1 H, s, H-3 of pyrrole), 5.09 (1 H, d, *J* 16.0 Hz, H_B), 5.03 (1 H, d, *J* 8.9 Hz, H_A), 2.73-2.70 (2 H, m, CH_2-7), 2.57-2.54 (2 H, m, CH_2-4), 1.83-1.76 (4 H, m, CH_2-5,6); δ_C (100.6 MHz, $CDCl_3$) 169.1, 157.5, 133.0, 130.6, 129.5, 128.0, 126.3, 121.2, 120.7, 112.8, 106.1, 106.0, 99.4, 22.3, 24.1, 23.5, 23.4.

4.7. Synthesis of 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)isoxazol-5(4*H*)-ones 18a-c (general procedure)

A solution of $NH_2OH{\cdot}HCl$ (2.088 g, 30 mmol) in H_2O (5 mL) was added to a solution of NaOH (1.2 g, 30 mmol) in H_2O (5 mL). This solution was added to ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propynoate **17a-c** (2.95 mmol) in DMSO (50 mL) and reaction mixture was stirred at 45-50 °C for 4 h, then cooled to room temperature, diluted with water (100 mL) and extracted with diethyl ether (1 x 30 mL), then with CH_2Cl_2 (8 x 30 mL). Dichloromethane extracts were washed with water and dried over Na_2SO_4. The residue, after removal of solvent, was recrystallized from acetone / H_2O (1:1) to afford target 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)isoxazol-5(4*H*)-one **18a-c** as light yellow solid.

*4.7.1. 3-(4,5,6,7-Tetrahydro-1H-indol-2-yl)isoxazol-5(4H)-one (**18a**).*

Yield 84%; yellow solid, mp 180-182 °C; [Found: C, 64.83; H, 5.56; N, 13.40. $C_{11}H_{12}N_2O_2$ requires C, 64.69; H, 5.92; N, 13.72%]; ν_{max}(KBr) 3279 (NH), 1806, 1793 (C=O), 1602 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 9.07 (1 H, br s, NH), 6.23 (1 H, s, H-3 of pyrrole), 3.69 (2 H, s, CH_2 of isoxazole), 2.60-2.58 (2 H, m, CH_2-7), 2.48-2.45 (2 H, m, CH_2-4), 1.82-1.77 (2 H, m, CH_2-5), 1.75-1.69 (2 H, m, CH_2-6); δ_C (100.6 MHz, $CDCl_3$) 174.7, 155.4, 134.3, 119.9, 117.1, 114.5, 34.0, 23.2, 22.8, 22.7, 22.5.

*4.7.2. 3-(1-Methyl-4,5,6,7-tetrahydro-1H-indol-2-yl)isoxazol-5(4H)-one (**18b**).*

Yield 87%; yellow solid, mp 160 °C; [Found: C, 66.25; H, 6.61; N, 13.05. $C_{12}H_{14}N_2O_2$ requires C, 66.04; H, 6.47; N, 12.84%]; ν_{max}(KBr) 1794 (C=O), 1602 (C=N) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 6.19 (1 H, s, H-3 of pyrrole), 3.72 (3 H, s, N-Me), 3.71 (2 H, s, CH_2 of isoxazole), 2.55-2.52 (2 H, m, CH_2-7), 2.48-2.45 (2 H, m, CH_2-4), 1.86-1.80 (2 H, m, CH_2-5), 1.73-1.67 (2 H, m, CH_2-6); δ_C (100.6 MHz, $CDCl_3$) 174.6, 156.4, 137.0, 119.5, 118.3, 114.9, 35.1, 33.3, 23.0, 22.7, 22.6, 22.0.

*4.7.3. 3-(1-Vinyl-4,5,6,7-tetrahydro-1H-indol-2-yl)isoxazol-5(4H)-one (**18c**).*

Yield 83%; yellow solid, mp 148 °C; [Found: C, 68.12; H, 6.32; N, 12.18. $C_{13}H_{14}N_2O_2$ requires: C, 67.81; H, 6.13; N, 12.17%]; ν_{max}(KBr) 1799 (C=O), 1642 (NCH=CH_2) cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 7.32 (1 H, dd, *J* 16.0, 9.0 Hz, H_X), 6.26 (1 H, s, H-3 of pyrrole), 5.10 (1 H, d, *J* 16.0 Hz, H_A), 5.08 (1 H, d, *J* 9.0 Hz, H_B), 3.71 (2 H, s, CH_2 of isoxazole), 2.68-2.65 (2 H, m, CH_2-7), 2.50-2.47 (2 H, m, CH_2-4), 1.82-1.76 (2 H, m, CH_2-5), 1.75-1.69 (2 H, m, CH_2-6); δ_C (100.6 MHz, $CDCl_3$) 174.4, 156.1, 136.2, 132.4, 121.2, 118.5, 116.7, 107.3, 35.2, 24.6, 23.1, 22.7, 22.6.

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