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Synthesis of novel indole substituted heterocyclics

Ponnam Devendar[#], A Niranjana Kumar[#], K V N S Srinivas* & J Kotesh Kumar*

Natural Product Chemistry Division, CSIR-Central Institute of Medicinal and Aromatic Plants, Research Centre, Boduppal, Hyderabad 500 092, India

E-mail: koteshkumarj@cimap.res.in; kvn.satyasrinivas@cimap.res.in

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Herein is reported the synthesis of a series (21 number) of novel hybrid molecules composed of an indole-3-carbaldehyde attached to triazole/ isoxazole/ isoxazoline moieties having various aromatic/benzylic/aliphatic substitutions *via* 1,3-dipolar cycloaddition between azide/ nitrile oxide (dipole) and indole substituted alkyne/ alkene (dipolarophile) based on the importance of indole, 1,2,3-triazole, isoxazole and isoxazoline containing pharmacophores.

Keywords: Indole 3-carbaldehye, 1,2,3-triazole, isoxazole, isoxazoline

Nature makes natural products of bewildering diversity and complexity and these are generally derived through specific biosynthetic pathways like, shikimate, polypeptide or mevalonate, leading to particular class of compounds[1]. Many biologically active natural products are also derived through mixed biosynthesis and have been found to exhibit unusual properties and biological activities. It led to the idea of generating novel molecular entities by rationally combining two or more different classes of compounds of natural or synthetic origin. Today, many natural product hybrids became new leads for drug discovery[2].

The indole ring is one of the most widely distributed heterocylces in nature. The indole nucleus is embedded in many biological systems including the essential amino acid tryptophan (I) (Figure 1). Another indole hybrid Serotonin plays a critical role in neuronal cell formation and maintenance, sleep, cognition, appetite, and mood, while melatonin is a natural bioregulator that induces and maintains sleep[3]. Indole nucleus is the basis of drugs like Indomethacin (II) (FDA approved in 1965, Figure 1), alkaloids and biologically active compound. Indole is a key sub structure in several natural compounds such as complex alkaloids, marine natural products and fungal metabolites as well as in pharmaceutical compounds such as naratriptan, zolmitriptan, rizatriptan, eletriptan, almotriptan, sumatriptan, frovatriptan and zafirlukast(III)[4]. As the indole scaffold has become one of the mostimportant structural subunits for drug discovery, more indole-containing drugs will be unearthed in the future. Indole 3-carbaldehyde (ICA), an indole-derived alkaloid, isolated from marine sponge *Smenospongia* sp[5]. It has been found to decrease biofilm formation in enter aggregative *E. coli* (EAEC) and *P. aeruginosa* by 11-fold and 2.3 fold, respectively[6].

During the last two decades, 1,2,3-triazoles have received the most considerations as pharmacophores in the drug discovery[7]. The synthetic 1,2,3-triazoles show diverse major biological activities, such as anticancer, antituberculosis, antivirus, etc[8]. Some of the semi-synthetic natural product 1,2,3-triazoles also showed different predominant biological activities, such as podophyllotoxin-1,2,3-triazoles (IV)[9], combretastatin A-4 triazoles[10], artemisinin 1,2,3-triazoles[11], dehydroabietic acid 1,2,3-triazoles[12].

Isoxazoles are class of compounds containing five membered azole ring, with an oxygen atom next to the nitrogen. These rings are found in some natural products such as ibotenic acid (V). (Figure 1) Isoxazoles also form the basis for a number of drugs/ pharmaceutical products including the COX-2 inhibitor valdecoxib (Bextra) (VI)[13]. These are potent selective agonists at human cloned dopamine D4 receptors[14] and exhibit gamma-amminobutyric acid-A antagonist[15], analgesic, anti-inflammatory, ulcerogenic, antimicrobial, antifungal, antinociceptive and anticancer activity[16].

# Ponnam Devendar and A Niranjana Kumar have equal contribution and considered as first authors.

Isoxazolines are another important class of five membered nitrogen-oxygen containing heterocyclic compounds that have been widely applied in medicinal and organic chemistry[17]. Many papers have accounted in the last decade for the synthesis and occurrence of 2-isoxazoline in Nature and medicinal chemistry. The most notable compounds are acivicin A (VII) and (+)-calafianin (A) and anticancer active (+)-calafianin (B) (VIII) (Figure 1). The nucleus is frequently found in natural products, bioactive molecules and can be used as bioisosteric transformations of amide bonds in order to provide metabolically stable and more active derivatives. Moreover, 2-Isoxazolines can be cleaved under various conditions to supply a variety of organic functionalities including γ-amino alcohols, β-amino acids, β-hydroxy ketones and β-hydroxy nitriles

The 1,3-dipolar cycloaddition reaction, sometimes referred to as Huisgen cycloaddition, has been known for over one hundred years[18]. Many studies on the regioselectivity of substituted triazoles/isoxazoles/ isoxazolines synthesis via 1,3-dipolarcycloaddition emphasized that substituted alkyne/alkene reacted with azide/ nitrile oxides. Nitrile oxides are reactive intermediates that are usually generated *in situ* from stable precursors. They can be generated from primary nitroalkane *via* dehydration or by a direct oxidation of aldoxime or halogenation of aldoxime to N-hydroxyliminoyl halides followed by dehydrohalogenation. The latter is the most usual method in nitrile oxide generation.

Viewing the importance of Indole, 1,2,3-triazoles, isoxazoles and isoxazolinescontaining pharmacophores, we synthesized a series of novel hybrid molecules composed of a Indole-3-carbaldehyde was connect with triazole/ isoxazoles/ isoxazolines moieties having various aromatic/ benzylic/ aliphatic substitutions *via* 1,3-dipolar cycloaddition between azide/nitrile oxide and indole substituted alkyne/alkene.

Results and Discussion

The present synthesis for target compounds was depicted in Scheme I and Scheme II. The key starting material Indole-3-carbaldehyde **1** and was alkylated with propargyl bromide/ allyl bromide using K_2CO_3 in DMF at room temperature, which gave corresponding *N*-propargyl indole-3-carbaldehye **2** / *N*-allyl indole 3-carbaldehye **5** respectively. The key Intermediates i.e., various substituted azides(***a-k***) and chloroximes (***l-p***) were prepared *in situ* as previous reported methods. The subtitled azides(***a-k***) are prepared from amine/halo precursors by diazotization/ nucleophilic substitution using NaN_3. Aldehydes converted in to corresponding oximes using NH_2OH/ EtOH, which upon converted into respective hydroximoyl chlorides/ chloroximes(***l-p***) using NCS/DMF[19].

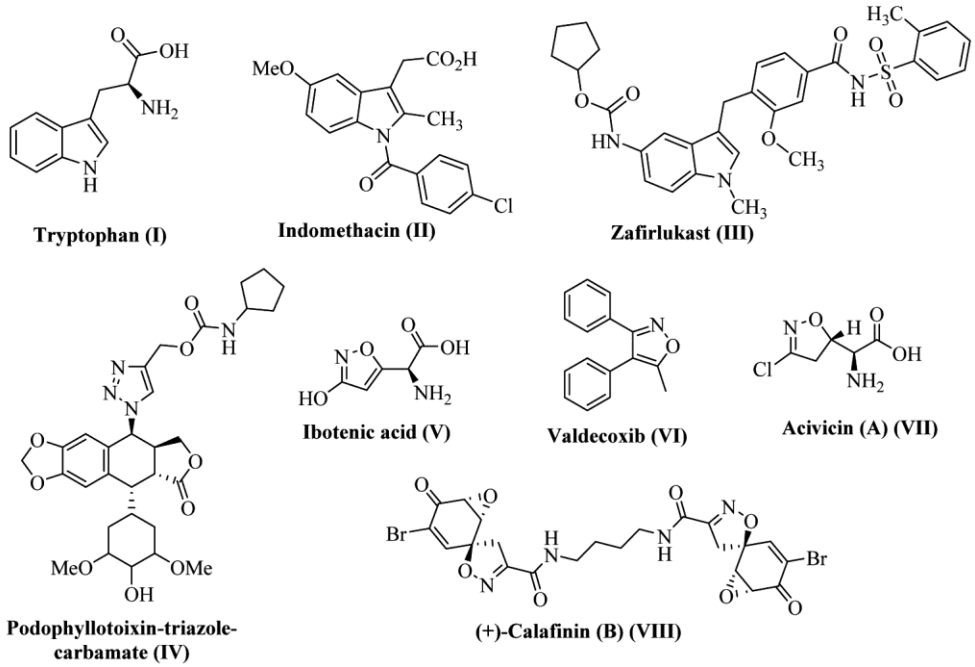


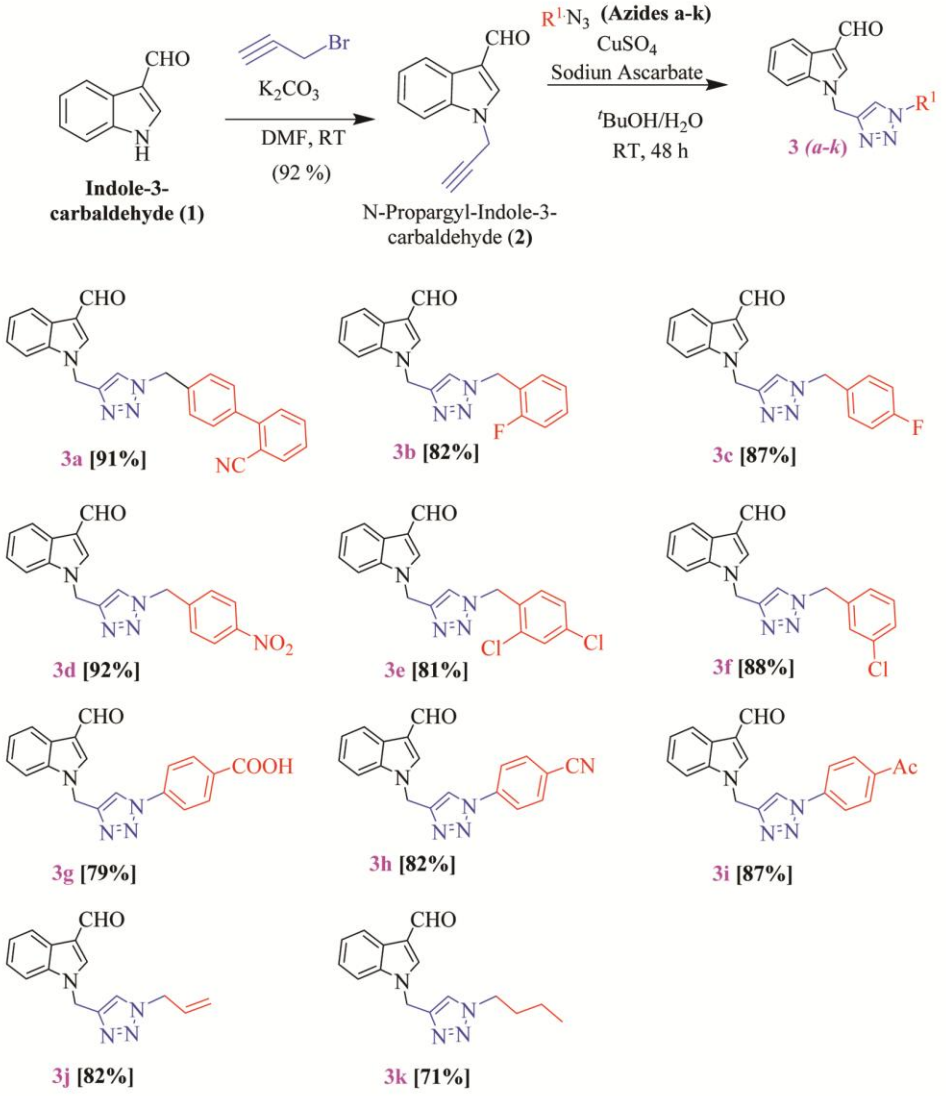
Figure 1 — Structures of bioactive natural and synthetic indole, triazole, isoxazoles and isoxazolines

The targeted Indole 1,4-disubstituted 1*H*-1,2,3-triazole hybrids **3a-k** were prepared by reacting of *N*-Propargyl indole 3-carbaldehyde **2** with various azides (**a-k**) in the presence of $CuSO_4.5H_2O$ and sodium ascorbate in *tert*-butanol and water mixture (1:1, click conditions) at RT for 24 h. The reaction mixture was diluted with water and cooled on ice, andthe precipitate was isolated by vacuum filtration and washed with cold water and cold *n*-hexane to afford crude compound. It was purified using flash column chromatography (silica gel 100-200 mesh) eluted with ethyl acetate: *n*-hexane (1:1) to afford pure compounds **3a-k** in 71-92 %yields (Scheme I).

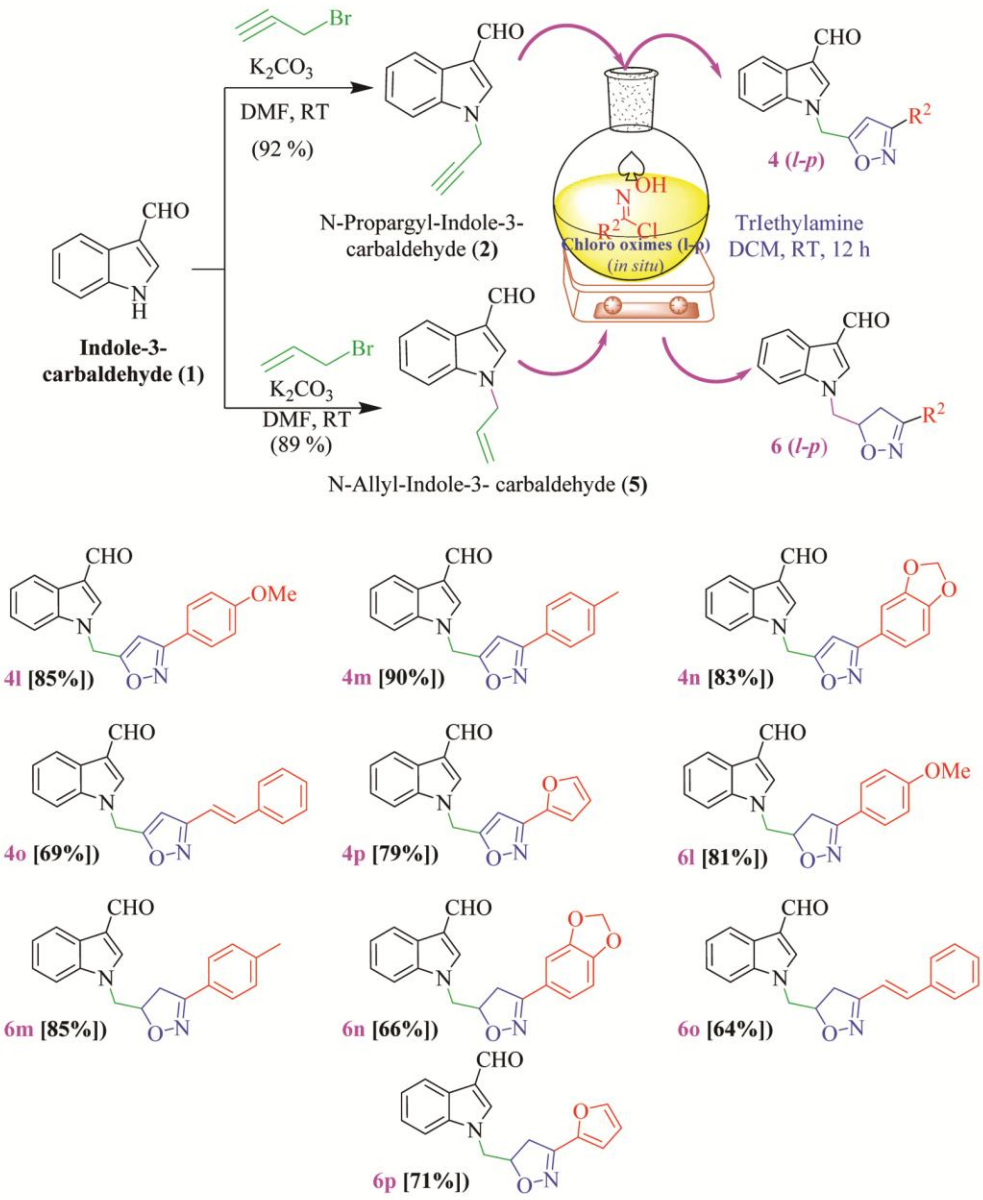
Also, the designed indoleisoxazoles **4(l-p)**/ isoxazolines**6(l-p)** were prepared by treating *N*-propargylindole-3-carbaldehyde**2**/ *N*-allyl-indole 3-carbaldehyde **5** with hydroximoyl chlorides (**l-p**, *in situ* generated) and triethyl amine in dichloromethane at RT for 12h in 64-90 % yields (Scheme II). The structure of these hybrids **3(a-k)**, **4(l-p)** and **6(l-p)** are assigned on thebasis of spectral data and analytical evidence (NMR, ESI-MS and IR data), and included in the Supplementary Information.

Experimental Section

All other chemicals and reagents purchased from Aldrich (India), AVRA Chemicals Pvt. Ltd. (India) and were used without further purification. TLC Silica gel 60 F_{254} (Merck, Germany) was used for TLC. Visualization of the developed



Scheme I — Synthesis of indole 1,2,3-triazole hybrids



Scheme II — Synthesis of Indole-Isoxazole/-Dihydroisoxazole hybrids

TLC was performed by UV light or 5% H_2SO_4 in MeOH stain.

Melting points were measured using a Kruss Optronic (Germany) melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Optics (Tensor 27 model, Germany) FT-IR spectrophotometer (using KBr pellets) and reported in wave number (cm^{-1}). ^1H NMR (300/400 MHz) and ^{13}C NMR (75/100 MHz) spectra were measured in $CDCl_3$ at room temperature on a Bruker Avance-III 300/400 MHz (Switzerland) instruments. The chemical shifts are reported as δ parts per million (ppm) in $CDCl_3$ (δ_H = 7.26; δ_C = 77.0) using tetramethylsilane as an internal standard. Data are reported as follows: chemical shift, multiplicity (s: singlet, d: doublet, t: triplet, dd: doublet of doublet, q: quartet, br: broad, m: multiplet), coupling constants (*J* in Hz) and integration.

General procedure for synthesis of indole-triazole hybrids 3a-k

To a solution of compound **2** (100 mg, 0.55 mmol), azide **a-k** (1.1 mmol) were suspended in 2:1 mixture of water and *tert*-Butyl alcohol (20 ml total volume).

Sodium ascorbate (0.16 mmol, 1M) and $CuSO_4.5H_2O$ (0.05 mmol, 0.1M) were added sequentially to the reaction mixture and the mixture was allowed to room temperature for next 48h. The reaction mixture was diluted with water (30 ml) and cooled on ice. The precipitate was isolated by vacuum filtration and washed with cold water (3 × 5 ml) and cold *n*-hexane (3 × 5 ml) to afford crude compound. It was purified using flash column chromatography (silica gel 100-200 mesh)eluted with ethyl acetate: *n*-hexane (1:1) to afford pure compounds **3a-k**.

4'-((4-((3-Formyl-1*H*-indol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)-[1,1'-biphenyl]-2-carbonitrile, 3a: Yield: 0.21 g (91 %), white solid, m.p. 108-110 °C; IR (KBr): 3121-3049 (=C-H), 2961-2762(C-H), 2225 (C≡N), 1738 (C=O), 1657 (C=C), 1576, 1534, 1462, 1393, 1168 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 10.0 (s, 1H, C*H*O), 8.32-8.29 (m, 1H, Ph-H), 7.84 (s, 1H, Pyrrole =C*H*), 7.79-7.63 (m, 2H, Ph-H), 7.56-7.53 (m, 2H, Ph-H + Triazole =C*H*), 7.49-7.43 (m, 3H, Ph-H), 7.36-7.31 (m, 5H, Ph-H), 5.54, 5.49 (2 ×s, 2 ×2H, Indole-N-CH_2-triazole-N-CH_2-Ph). ESI-MS: positive ion mode: *m/z* = 418.1$[M+H]^+$, 440.06 $[M+Na]^+$(calculated mass M for $C_{26}H_{19}N_5O$ is 417.16).

1-((1-(2-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-indole-3-carbaldehyde, 3b: Yield: 0.15 g (82 %), white solid, m.p. 118-120 °C; IR (KBr): 3145-3112 (=C-H), 2970-2724(C-H), 1738 (C=O), 1659 (C=C), 1587, 1531, 1492, 1391 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 10.0 (s, 1H, C*H*O), 8.30-8.26 (m, 1H, Ar-H), 7.79 (s, 1H, pyrrole =C*H*), 7.45-7.40 (m, 2H, Ph-H + triazole =C*H*), 7.36-7.29 (m, 3H, Ph-H), 7.25-7.22 (m, 1H, Ph-H), 7.15-7.06 (m, 2H, Ph-H), 5.52, 5.45 (2 ×s, 2 ×2H, Indole-N-CH_2-triazole-N-CH_2-Ph). ESI-MS: positive ion mode: *m/z* = 357.24 $[M+Na]^+$ (calculated mass M for $C_{19}H_{15}FN_4O$ is 334.12).

1-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-indole-3-carbaldehyde, 3c: Yield: 0.16 g (87 %), white solid, m.p. 140-142 °C; IR (KBr): 3121-3082 (=C-H), 2827 (C-H), 1739 (C=O), 1648 (C=C), 1603, 1510, 1406, 1227, 1156, 1037 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 9.99 (s, 1H, C*H*O), 8.32-8.28 (m, 1H, Ar-H), 7.79 (s, 1H, pyrrole =C*H*), 7.42-7.38 (m, 1H, Ph-H), 7.34-7.30 (m, 2H, Ar-H), 7.23-7.19 (m, 3H, Ph-H), 7.06-7.0 (m, 2H, Ph-H), 5.46 & 5.43 (2 ×s, 2 × 2H, Indole-N-CH_2-triazole-N-CH_2-Ph). ESI-MS: positive ion mode: *m/z* = 357.2 $[M+Na]^+$ (calculated mass M for $C_{19}H_{15}FN_4O$ is 334.12).

1-((1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-indole-3-carbaldehyde, 3d: Yield: 0.18 g (92 %), Yellow solid, m.p. 108-110 °C; IR (KBr): 3146-3077 (=C-H), 2949-2827 (C-H), 1738 (C=O), 1644 (C=C), 1610, 1581 (N=N), 1521 (N-O sym), 1466, 1427, 1392, 1344 (N-O asym), 1147 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 9.98 (s, 1H, C*H*O), 8.31-8.28 (m, 1H, Ar-H), 8.21-8.18 (d, *J* = 8.7 Hz, 2H, Ph-H), 7.82 (s, 1H, pyrrole =C*H*), 7.42-7.30 (m, 6H, Ph-H), 5.57 & 5.50 (s each, 2H each, Ph-CH_2 and Indole N-CH_2). ESI-MS: positive ion mode: *m/z* = 362.06 $[M+H]^+$(calculated mass M for $C_{19}H_{15}N_5O_3$ is 361.12).

1-((1-(2,4-Dichlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-indole-3-carbaldehyde, 3e: Yield: 0.17 g (81 %), white solid, m.p. 98-100 °C; IR (KBr): 3140-3028 (=C-H), 2949 (C-H), 2818-2760 (aldehyde C-H), 1740 (C=O), 1659 (C=C), 1590, 1534, 1392, 1356, 1160 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 10.0 (s, 1H, C*H*O), 8.32-8.29 (m, 1H, Ar-H), 7.82 (s, 1H, pyrrole =C*H*), 7.44-7.40 (m, 2H, Ph-H), 7.39 (s, 1H, triazole =C-H),7.34-7.31 (m, 2H, Ph-H), 7.23-7,22 (d, *J* = 2.1 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H, Ph-H), 5.57, 5.48 (2 ×s, 2 ×2H, Indole-N-CH_2-triazole-N-CH_2-Ph). ESI-MS: positive ion mode: *m/z* = 384.95 $[M+H]^+$, 406.90 $[M+Na]^+$,408.90 $[M+2+Na]^+$,791.10 $[M+2Na]^+$, $[M+2+2Na]^+$, (calculated mass M for $C_{19}H_{14}Cl_2N_4O$ is 384.05).

1-((1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-indole-3-carbaldehyde, 3f: Yield: 0.17 g (88 %), white solid, m.p. 118-120 °C; IR (KBr): 3126-3074 (=C-H), 2963 (C-H), 2815-2759 (aldehyde C-H), 1739 (C=O), 1649 (C=C), 1578, 1530, 1465, 1392, 1160 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 9.98 (s, 1H, C*H*O), 8.31-8.27 (m, 1H, Ar-H), 7.81 (s, 1H, pyrrole =C*H*), 7.40 (s, 1H, triazole =C-H),7.33-7.28 (m, 5H, Ph-H), 7.21-7,19 (m, 1H, Ph-H), 7.11-7.08 (m, 1H, Ph-H), 5.47, 5.44 (2 ×s, 2 ×2H, Indole-N-CH_2-triazole-N-CH_2-Ph). ESI-MS: positive ion mode: *m/z* = 373.08 $[M+Na]^+$ (calculated mass M for $C_{19}H_{15}ClN_4O$ is 350.09).

4-(4-((3-Formyl-1*H*-indol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)benzoic acid, 3g: Yield: 0.15 g (79 %), white solid, m.p. 220-222 °C; IR (KBr): 3782 (O-H), 3109-3066 ((=C-H), 2921 (C-H), 2810-2760 (aldehyde C-H), 1713 (C=O), 1642, 1461, 1260, 1167 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 13.443 (br. s, 1H, COO*H*), 9.95 (s, 1H, C*H*O), 9.06 (s, 1H,

triazole =C-H), 8.46 (s, 1H, pyrrole =C*H*), 8.73 (*t*, *J* = 1.8 Hz, 1H, Ph-H), 8.16-8.01 (m, 2H, Ph-H), 8.02 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.77 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.71 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.36-7.24 (m, 2H, Ph-H), 5.71 (s, 2H, N-CH_2). ESI-MS: positive ion mode: *m/z* = 347.03 $[M+H]^+$ (calculated mass M for $C_{19}H_{14}N_4O_3$ is 346.11).

4-(4-((3-Formyl-1*H*-indol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)benzonitrile, 3h: Yield: 0.14 g (82 %), Brown solid, m.p. 172-174 ℃; IR (KBr): 3098 (Phenyl =C-H), 2971 (C-H), 2870-2818 (aldehyde C-H), 2227 (C≡N), 1739 (C=O), 1653 (C=C), 1530, 1347, 1170 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 9.99 (s, 1H, C*H*O), 8.32-8.30 (m, 1H, Ph-*H*), 7.86-7.78 (m, 5H, Ph-H), 7.48 (s, 1H, pyrrole =C*H*), 7.35-7.33 (m, 3H, Ar-H), 5.59 (s, 2H, N-CH_2). ESI-MS: positive ion mode: *m/z* = 328.06 $[M+H]^+$, 350.02 $[M+Na]^+$ (calculated mass M for $C_{19}H_{13}N_5O$ is 327.11).

1-((1-(4-Acetylphenyl)-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-indole-3-carbaldehyde, 3i: Yield: 0.16 g (87 %), White solid, m.p. 198-200 °C; IR (KBr): 3160-3094 (Phenyl =C-H), 2998-2917 (C-H), 2797-2717 (aldehyde C-H), 1738 (C=O), 1656 (C=C), 1604, 1531, 1467, 1388, 1171 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 10.03 (s, 1H, C*H*O), 8.34-8.31 (m, 1H, Ph-*H*), 8.09 (d, *J* = 8.7 Hz, 2H, Ph-H), 7.48 (s, 1H, pyrrole =C*H*), 7.79 (d, *J* = 8.7 Hz, 2H, Ph-H), 7.51-7.48 (m, 1H, Ph-H), 5.60 (s, 2H, N-CH_2), 7.39-7.34 (m, 2H, Ph-H),2.67 (s, 3H, $COCH_3$). ESI-MS: positive ion mode: *m/z* = $[M+H]^+$, $[M+Na]^+$, calculated mass (M) for $C_{20}H_{16}N_4O_2$ = is 344.13.

1-((1-Allyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole-3-carbaldehyde, 3j: Yield: 0.12 g (82 %), Pale yellow solid, m.p. 78-80 °C; IR (KBr): 3143-3059 (Phenyl =C-H), 2997-2937 (C-H), 2824-2763 (aldehyde C-H), 1739 (C=O), 1649 (C=C), 1577, 1529, 1462, 1391, 1159 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 9.99 (s, 1H, C*H*O), 8.32-8.29 (m, 1H, Ph-*H*), 7.82 (s, 1H, pyrrole =C*H*), 7.437 (s, 1H, triazole =C-*H*), 7.36-7.31 (m, 3H, Ph-H), 6.02-5.91 (m, 1H, N-CH_2-C*H*=CH_2), 5.49 (s, 2H, N- CH_2),5.34 (d, *J* = 10.2 Hz, 2H, N_3-CH_2-CH=CH_2), 5.27 (d, *J* = 17.1 Hz, 2H, N_3-CH_2-CH=CH_2), 4.92 (d, *J* = 6.3 Hz, 2H, N_3-CH_2-CH=CH_2). ESI-MS: positive ion mode: *m/z* = 289.10 $[M+Na]^+$, 555.3 $[M+2Na]^+$ (calculated mass M for $C_{15}H_{14}N_4O$ is 266.12).

1-((1-Butyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole-3-carbaldehyde, 3k: Yield: 0.11 g (71 %), Yellow solid, m.p. 60-62 °C; IR (KBr): 3147-3111 (=C-H), 2961-2834 (C-H), 1739 (C=O), 1651 (C=C), 1529, 1465, 1391, 1158 cm^{-1}. NMR (300 MHz, $CDCl_3$): δ_H (ppm) 10.0 (s, 1H, C*H*O), 8.33-8.30 (m, 1H, Ph-*H*), 7.83 (s, 1H, pyrrole =C*H*), 7.43 (s, 1H, triazole =C-H), 7.37-7.32 (m, 3H, Ph-H), 5.49 (s, 2H, N-CH_2), 4.29 (t, *J* = 7.2 Hz, 2H, N_3-CH_2-CH_2-CH_2-CH_3), 1.88-1.79 (m, 2H, N_3-CH_2-CH_2-CH_2-CH_3), 1.35-1.25 (m, 2H, N_3-CH_2-CH_2-CH_2-CH_3), 0.92 (t, *J* = 7.5 Hz, 3H, N_3-CH_2-CH_2-CH_2-CH_3). ESI-MS: positive ion mode: *m/z* = 283.03 $[M+H]^+$ (calculated mass (M) for $C_{16}H_{18}N_4O$ is 282.15).

General procedure for synthesis of indole-isoxazole hybrids 4l-p

To a solution of 1-propargyl-indole-3-carbaldehe **2** (100 mg, 0.55 mmol) and chloro oximes/ hydroximoylchlorides***l-p***(1.1 mmol) in DCM was added triethylamine (0.82 mmol) in drop wise under nitrogen atmosphere. The mixture was stirred at RT for 12 h, quenched with water (10 ml) and the product extracted in to DCM (3 x 10 ml). The combined organic layers were washed with water and brine successively, dried over Na_2SO_4 and solvent removed under reduced pressure. The obtained crude product was further purified by silica gel (100-200 mesh) flash column chromatography using DCM in MeOH (2%) as eluent to obtain desired products **4**(***l-p***).

1-((3-(4-Methoxyphenyl)isoxazol-5-yl)methyl)-1*H*-indole-3-carbaldehyde, 4l: Yield: 0.15 g (85 %), Colorless solid, m.p. 120-122 °C; IR (KBr): 3118-3013 (=C-H), 2971 (C-H), 2811-2777 (aldehyde C-H), 1740 (C=O), 1654 (C=C), 1571, 1528, 1461, 1371, 1216, 1134 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) 10.04 (s, 1H, C*H*O), 8.35-8.33 (m, 1H, Ph-H), 7.82 (s, 1H, pyrrole =C*H*), 7.65 (d, *J*= 6.9 Hz, 2H, Ph-H), 7.40-7.34 (m, 3H, Ph-H), 6.92 (d, *J* = 6.9 Hz, 2H, Ph-H), 6.30 (s, 1H, Isoxazole =CH), 5.49 (s, 2H, N-CH_2), 3.82 (s, 3H, OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ_c (ppm) 184.57, 166.30, 162.33, 161.25, 137.96, 136.98, 128.1 (×2), 125.32, 124.60, 123.37, 122.35, 120.60, 119.26, 114.3 (×2), 109.77, 101.05, 55.30, 42.62. ESI-MS: positive ion mode: *m/z* = 333.15 $[M+H]^+$, 355.12 $[M+Na]^+$ (calculated mass M for $C_{20}H_{16}N_2O_3$ is 332.12).

1-((3-(*p*-Tolyl)isoxazol-5-yl)methyl)-1*H*-indole-3-carbaldehyde, 4m: Yield: 0.15 g (90 %), White solid, m.p. 120-132 °C; IR (KBr): 3110 (Phenyl =C-H), 2988 (C-H), 2816 (aldehyde C-H), 1796 (C=O), 1648 (C=C), 1576, 1530, 1450,1371, 1163 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.01 (s, 1H, C*H*O),

8.32- 8.30 (m, 1H, Ph-H), 7.79 (s, 1H, pyrrole =C*H*), 7.57 (d, *J*= 8.0 Hz, 2H, Ph-H), 7.39-7.29 (m, 3H, Ph-H), 7.18 (d, *J* = 8.0 Hz, 2H, Ph-H), 6.31 (s, 1H, Isoxazole =CH), 5.46 (s, 2H, N-CH_2), 2.34 (s, 3H, Ph-CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_c (ppm) 184.65, 166.43, 162.75, 140.61, 138.0, 137.0, 129.6 (×2) 126.6 (×2), 125.39, 125.33, 124.68, 123.45, 122.44, 119.34, 109.80, 101.26, 42.70, 21.40. ESI-MS: positive ion mode: *m/z* = 317.02 $[M+H]^+$, 339 $[M+Na]^+$ (calculated mass (M) for $C_{20}H_{16}N_2O_2$ is 316.12).

1-((3-(Benzo[*d*][1,3]dioxol-4-yl)isoxazol-5-yl)methyl)-1*H*-indole-3-carbaldehyde, 4n: Yield: 0.15 g (83 %), White solid, m.p. 92-94 °C; IR (KBr): 3159 (=C-H), 3002 (C-H), 2817 (aldehyde C-H), 1790 (C=O), 1649 (C=C), 1610, 1506, 1461, 1394, 1158 cm^{-1}. NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.04 (s, 1H, C*H*O), 8.34- 8.32 (m, 1H, Ph-H), 7.84 (s, 1H, pyrrole =C*H*), 7.44-7.34 (m, 3H, Ar-H), 7.12 (s, 1H, Piperonal Ar-H), 6.60 (s, 1H, Isoxazole =C*H*), 7.12-6.89 (m, 2H, Ar-H), 6.02 (s, 2H, *O*-CH_2-*O*), 5.51 (s, 2H, Indole N-CH_2). ESI-MS: positive ion mode: *m/z* = 347 $[M+H]^+$ calculated mass (M) for $C_{20}H_{14}N_2O_4$ is 346.

(E)-1-((3-Styrylisoxazol-5-yl)methyl)-1*H*-indole-3-carbaldehyde, 4o: Yield: 0.12 g (69 %), Pale yellow solid, m.p. 144-146°C; IR (KBr): 3136-3106 (=C-H), 2922 (C-H), 28107-2754 (aldehyde C-H), 1657 (C=C), 1608, 1530, 1434,1389, 1165 cm^{-1}. ESI-MS: positive ion mode: *m/z* = 351 $[M+H]^+$ (Calculated Mass M for $C_{21}H_{16}N_2O_2$ is 328.12).

1-((3-(Furan-2-yl)isoxazol-5-yl)methyl)-1*H*-indole-3-carbaldehyde, 4p: Yield: 0.12 g (79 %), Brown solid, m.p. 130-132°C; IR (KBr): 3124 (=C-H), 3024 (C-H), 2810-2754 (aldehyde C-H), 1784 (C=O), 1655 (C=C), 1613, 1528, 1492,1393, 1193 cm^{-1}. NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.06 (s, 1H, C*H*O), 8.37- 8.35 (m, 1H, Ph-H), 7.83 (s, 1H, pyrrole =C*H*), 7.42-7.28 (m, 4H, Ar-H), 6.88 (d, *J* = 3.6 Hz, Furfural =C*H*), 6.51 (dd, *J* = 3.6, 2.0 Hz, Furfural =C*H*), 6.3 (s, 1H, Isoxazole =C*H*), 5.52 (s, 2H, Indole N-CH_2). ESI-MS: positive ion mode: *m/z* = 293.05 $[M+H]^+$ (calculated mass M for $C_{17}H_{12}N_2O_3$ is 292.08).

Synthesis and spectral data of *N*-allyl-Indole-3-carbaldehyde, 5

To a solution of indole-3-carbaldehyde (0.72 g, 5 mmol) and potassium carbonate (1.04 g, 7.5 mmol) in DMF (20 mL), allyl bromide (0.86 mL, 10 mmol) was added drop wise at RT and this solution was stirred at room temperature overnight. After completion of reaction, the reaction mixture was partitioned between DCM (40 mL) and water (30 mL), the DCM layer was collected. The aqueous layer was extracted three times with DCM (3 ×20 mL), the combined organic extracts was dried over anhydrous Na_2SO_4, concentrated under vacuum and it was crystalized using isopropyl alcohol and water (10:90) to obtain the desired product. Yield: 0.81 g (90 %), white solid, m.p. 74-76 °C; IR (KBr): 3196 (Ar C-H), 1739 (C=O), 1640 (C=C)cm^{-1}.NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.0 (s, 1H, C*H*O), 8.32-8.30 (m, 1H, Ar 4-H), 7.72 (s, 1H, Indole 2-H), 7.36-7.31 (m, 3H, Ar 5-H, 6-H, 7-H), 6.07–5.97 (m, 1H, NCH_2CH=CH_2), 5.32 (dt, *J* = 10.4, 1.2 Hz, 1H, NCH_2CH=CH_2) 5.19 (dt, *J* = 17.2, 1.2 Hz, 1H, NCH_2CH=CH_2), 4.78 (dt, *J* = 5.6, 1.2 Hz, 2H, NCH_2). ESI-MS: positive ion mode: *m/z* = 183.07 $[M+H]^+$, [M + Na]+ calculated mass (M) for $C_{12}H_9NO$ is 183.07.

General procedure for synthesis of indole-dihydroisoxazole hybrids, 6l-p

To a solution of 1-allyl-indole-3-carbaldehe **5** (100 mg, 0.54 mmol) and hydroximoyl chlorides ***l-p*** (1.1 mmol) in DCM was added triethylamine (0.82 mmol) in drop wise under nitrogen atmosphere. The mixture was stirred at RT for 12 h, quenched with water (10 mL) and the product extracted into DCM (3 x 10 mL). The combined organic layers were washed with water and brine successively, dried over Na_2SO_4 and solvent removed under reduced pressure. The obtained crude product was further purified by silica gel (100-200 mesh) flash column chromatography using DCM in MeOH (2%) as eluent to obtain desired products **6l-p**.

1-((3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-yl) methyl)-1*H*-indole-3-carbaldehyde, 6l: Yield: 0.14 g (81 %), White solid, m.p. 128-130°C; IR (KBr): 3016 (=C-H), 2970 (C-H), 2805-2726 (aldehyde C-H), 1740 (C=O), 1655 (C=C), 1607, 1533, 1466, 1367, 1230, 1139 cm^{-1}. NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.0 (s, 1H, C*H*O), 8.33-8.31 (m, 1H, Ph-*H*), 7.88 (s, 1H, pyrrole =C*H*), 7.56 (d, *J* = 8.8 Hz, 2H, Ph-H), 7.40-7.32 (m, 3H, Ph-H), 6.89 (d, *J* = 6.9 Hz, 2H, Ph-H), 5.11-5.07 (m, 1H, Isoxazoline ring *O*-C*H*-CH_2), 4.38 (d,*J* = 5.2 Hz, 2H, Indole N-CH_2-CH), 3.92 (s, 3H, *OC*H_3), 3.45 (dd, *J* = 16.4, 10.4 Hz, 1H, Isoxazoline *O*-CH-CH_2), 3.05 (dd, *J* = 16.4, 7.2 Hz, 1H, Isoxazoline*O*-CH-CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_c (ppm) 184.69, 161.37, 156.16, 139.22,

137.42, 128.5 (×2), 125.19, 124.19, 123.02, 122.30, 121.12, 118.78, 114.5 (×2), 109.62, 78.55, 55.31, 49.43, 38.16. ESI-MS: positive ion mode: *m/z* = 335.28 $[M+H]^+$, 357.21 $[M+Na]^+$ (calculated mass M for $C_{20}H_{18}N_2O_3$ is 334.13).

1-((3-(*p*-Tolyl)-4,5-dihydroisoxazol-5-yl)methyl)-1*H*-indole-3-carbaldehyde, 6m: Yield: 0.14 g (85 %), White solid, m.p. 130-132°C; IR (KBr): 3110 (=C-H), 2988-2939 (C-H), 2816-2761 (aldehyde C-H), 1796 (C=O), 1648 (C=C), 1610, 1530, 1450, 1367, 1249, 1163 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.03 (s, 1H, C*H*O), 8.35- 8.33 (m, 1H, Ph-H), 7.90 (s, 1H, pyrrole =C*H*), 7.57 (d, *J* = 8.0 Hz, 2H, Ph-H), 7.44-7.33 (m, 3H, Ph-H), 7.21 (d, *J* = 8.0 Hz, 2H, Ph-H), 5.15-5.11 (m, 1H, Isoxazoline*O*-C*H*-CH_2), 4.41 (d,*J* = 5.6 Hz, 2H, Indole N-CH_2-CH), 3.48 (dd, *J* = 16.8, 10.4 Hz, 1H, Isoxazoline*O*-CH-CH_2), 3.08 (dd, *J* = 16.4, 7.2 Hz, 1H, Isoxazoline*O*-CH-CH_2), 2.39 (s, 3H, Ph-CH_3). ESI-MS: positive ion mode: *m/z* = 340.98 $[M+Na]^+$ (calculated mass M for $C_{20}H_{18}N_2O_2$ is 318.14).

1-((3-(Benzo[d][1,3]dioxol-4-yl)-4,5-dihydroisoxazol-5-yl)methyl)-1*H*-indole-3-carbaldehyde, 6n: Yield: 0.12 g (66 %), Pale yellow solid, m.p. 184-186 °C; IR (KBr): 3114 (=C-H), 2907 (C-H), 2811 (aldehyde C-H), 1702 (C=O), 1643 (C=C), 1612, 1529, 1449, 1396, 1160 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.01 (s, 1H, C*H*O), 8.39-8.31 (m, 1H, Ar-H), 7.89 (s, 1H, Pyrrole =C*H*), 7.42-7.22 (m, 4H, Ar-H), 6.95 (dd, 1H, *J* = 8.0, 1.6 Hz, Piperonal =C*H*), 6.79 (d, 1H, *J* = 8.0 Hz, Piperonal =C*H*), 6.01 (s, 2H, *O*-CH_2-*O*), 5.14-5.07 (m, 1H, Isoxazoline O-C*H*-CH_2), 4.39 (d, *J* = 5.2 Hz, Indole N-CH_2), 3.43 (dd, *J* = 16.8, 10.4 Hz, 1H, Isoxazoline*O*-CH-CH_2), 3.03 (dd, *J* = 16.4, 7.2 Hz, 1H, Isoxazoline*O*-CH-CH_2).). ESI-MS: positive ion mode: *m/z* = 349.07 $[M+H]^+$ calculated mass (M) for $C_{20}H_{16}N_2O_4$ is 348.11.

(E)-1-((3-Styryl-4,5-dihydroisoxazol-5-yl)methyl)-1*H*-indole-3-carbaldehyde, 6o: Yield: 0.11 g (64 %), White solid, m.p. 140-142 °C; IR (KBr): 3014 (=C-H), 2970 (C-H), 2812 (aldehyde C-H), 1740 (C=O), 1657 (C=C), 1612, 1528, 1467,1369, 1161 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H (ppm) 10.03 (1H, s, C*H*O), 8.34-8.32 (m, 1H, Ar-H), 7.88 (1H, s, Pyrrole =C*H*), 7.44-7.33 (m, 8H, Ar-H), 7.03 (d, 1H, *J* = 16.4 Hz, Ph-CH=C*H*), 6.69 (d, 1H, *J* = 16.4 Hz, Ph-C*H*=CH), 5.12-5.05 (m, 1H, Isoxazoline*O*-C*H*-CH_2), 4.38 (d, *J* = 5.2 Hz, Indole N-CH_2), 3.33 (dd, *J* = 16.8, 10.4 Hz, 1H, Isoxazoline O-CH-CH_2), 2.94 (dd, *J* = 16.4, 7.2 Hz, 1H, Isoxazoline*O*-CH-CH_2). ESI-MS: positive ion mode: *m/z* = $[M+H]^+$, $[M+Na]^+$, calculated mass (M) for $C_{21}H_{18}N_2O_2$ is 330.14.

1-((3-(Furan-2-yl)-4,5-dihydroisoxazol-5-yl) methyl)-1*H*-indole-3-carbaldehyde, 6p: Yield: 0.11 g (71 %), White solid, m.p. 142-144 °C; IR (KBr): 3124 (=C-H), 3024 (C-H), 2810-2754 (aldehyde C-H), 1784 (C=O), 1655 (C=C), 1613, 1528, 1492, 1393, 1193 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H (ppm) 10.03 (s, 1H, C*H*O), 8.35- 8.32 (m, 1H, Ph-H), 7.87 (s, 1H, pyrrole =C*H*), 7.41-7.28 (m, 4H, Ar-H), 6.70 (d, *J* = 3.6 Hz, 1H, Furfural-C*H*), 6.28 (d, *J* = 3.6 Hz, Furfural-C*H*),5.16-5.07 (m, 1H, Isoxazoline O-C*H*-CH_2), 4.40 (d,*J* = 6.0 Hz, 2H, Indole N-CH_2-CH), 3.42 (dd, *J* = 16.8, 10.5 Hz, 1H, Isoxazoline. ESI-MS: positive ion mode: *m/z* = 317.01 $[M+Na]^+$ (calculated mass M for $C_{17}H_{14}N_2O_3$ is 294.10).

Conclusion

In conclusion, we described a convenient and efficient method for the synthesis of novel hybrids i.e., Indole-3-carbaldehyde with 1,4-disubstituted1,2,3-triazoles, 3,5-difunctionalized isoxazoles/-isoxazolines by using 1,3-dipolarcycloadditon reaction as a key step. The predictable regiochemistry and stereochemistry of cycloaddition, and the generally high yields of cycloadducts, ensure that this will find a widespread application in the area organic and medicinal chemistry.

Supplementary Information

Supplementary information is available in the websitehttp://nopr.niscair.res.in/handle/123456789/58776.

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Disclosure statement

The authors declare no competing financial interest.

References

1 Somei M, Aoki N & Nakagawa K, *Heterocycles*, 38(7) (1994) 1479. DOI: 10.3987/COM-94-6738.

2 Tietze L F, Bell H P & Chandrasekhar S, *Chemie Int Ed*, 42(34) (2003) 3996. DOI: 10.1002/anie.200200553.

3 De Sa A, Fernando R, Barreiro E J, Fraga M & Alberto C, *Mini Rev Med Chem*, 9(7) (2009) 782. DOI: 10.2174/138955709788452649.

4 Kochanowska Karamyan A J & Hamann M T, *Chem Rev*, 110(8) (2010) 4489. DOI: 10.1021/cr900211p.

5 McKay M J, Carroll A R, Quinn R J & Hooper J N A, *J Nat Prod*, 65(4) (2002) 595. DOI: 10.1021/np010347v.

6 Bommarius B, Anyanful A, Izrayelit Y, Bhatt S, Cartwright E, Wang W, Swimm A I, Benian G M, Schroeder F C & Kalman D A, *PLoS One*, 8(1) (2013) e54456. DOI: 10.1371/journal.pone.0054456.

7 Agalave S G, Maujan S R & Pore V S, *Chem An Asian J*, 6(10) (2011) 2696. DOI: 10.1002/asia.201100432.

8 Soltis M J, Yeh H J, Cole K A, Whittaker N, Wersto R P & Kohn E C, *Drug Metab Dispos*, 24(7) (1996) 799.

9 Reddy D M, Srinivas J, Chashoo G, Saxena A K & Sampath Kumar H M, *Eur J Med Chem*, 46(6) (2011) 1983. DOI: 10.1016/j.ejmech.2011.02.016.

10 Odlo K, Fournier DitChabert J, Ducki S, Gani O A B S M, Sylte I & Hansen T V, *Bioorg Med Chem*, 18(18) (2010) 6874. DOI: 10.1016/j.bmc.2010.07.032.

11 Lee S J, *Bull Korean Chem Soc*, 32(2) (2011) 737. DOI: 10.5012/bkcs.2011.32.2.737.

12 Pertino M W, Verdugo V, Theoduloz C & Schmeda Hirschmann G, *Molecules*, 19(2) (2014) 2523. DOI: 10.3390/molecules19022523.

13 Talley J J, Brown D L, Carter J S, Graneto M J, Koboldt C M, Masferrer J L, Perkins W E, Rogers R S, Shaffer A F, Zhang Y Y, Zweifel B S & Seibert K, *J Med Chem*, 43(5) (2000) 775. DOI: 10.1021/jm990577v.

14 Rowley M, Broughton H B, Collins I, Baker R, Emms F, Marwood R, Patel S, Patel S, Ragan C I, Freedman S B & Leeson P D, *J Med Chem*, 39(10) (1996) 1943. DOI: 10.1021/jm960072u.

15 Frølund B, Jørgensen A T, Tagmose L, Stensbøl T B, Vestergaard H T, Engblom C, Kristiansen U, Sanchez C, KrogsgaardLarsen P & Liljefors T, *J Med Chem*, 45(12) (2002) 2454. DOI: 10.1021/jm020027o.

16 Li W T, Hwang D R, Chen C P, Shen C W, Huang C L, Chen T W, Lin C H, Chang Y L, Chang Y Y, Lo Y K, Tseng H Y, Lin C C, Song J S, Chen H C, Chen S J, Wu S & Chen C T, *J Med Chem*, 46(9) (2003) 1706. DOI: 10.1021/jm020471r.

17 Paul Savage G, *Curr Org Chem*, 14(14) (2010) 1478. DOI: 10.2174/138527210791616812.

18 Kolb H C, Finn M G & Sharpless K B, *Angew Chem Int Ed*, 40(11) (2001) 2004. DOI: 10.1002/1521-3773 (20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5.

19 Larsen K E & Torssell K B G, *Tetrahedron*, 40(15) (1984) 2985. DOI: 10.1016/S0040-4020(01)91313-4.