Copper-catalyzed Synthesis of *N*-alkylated 2-(4-substituted-1*H*-1,2,3-triazol-1-yl)-1*H*-indole-3-carbaldehyde by Step-wise and One-pot Three-component Huisgen's 1,3-dipolar Cycloaddition Reaction

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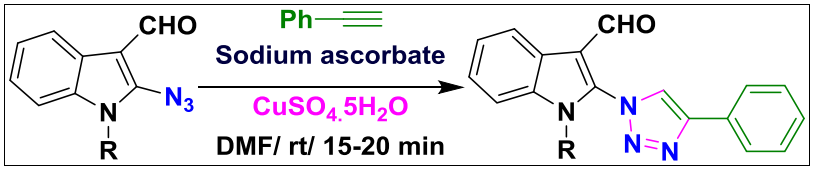

An efficient method for the synthesis of *N*-alkylated 2-(4-substituted-1*H*-1,2,3-triazol-1-yl)-1*H*-indole-3-carbaldehyde has been developed starting from oxindole and indole using Huisgen's 1,3-dipolar cycloaddition reaction of organic azides to alkynes. The effect of catalysts and solvent on these reactions has been investigated. Among all these conditions, while using $CuSO_4{\cdot}5H_2O$, DMF was found to be the best system for this reaction. It could also be prepared in a one-pot three-component manner by treating equimolar quantities of halides, azides, and alkynes. The Huisgen's 1,3-dipolar cycloaddition reaction was performed using $CuSO_4{\cdot}5H_2O$ in DMF with easy work-up procedure.

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INTRODUCTION

Oxindole derivatives [1] have demonstrated significant potential for use in a wide range of biological applications such as NMDA antagonist [2], calcium channel blockers [3], antiangiogenic [4], anticancer [5], and analgesic effects [6]. The indole nucleus is the core structure in a great number of tubulin polymerization inhibitors [7,8]. Indole [9] is the parent substance of a large number of important compounds that occur in nature. Synthetic indole alkaloids with different substitutions at the C-1, C-6, and C-7 positions, some of which are widely distributed in many plants and mammals and exhibit a wide spectrum of biological activities [10,11].

1,2,3-Triazoles are important heterocycles [12], which are widely used in pharmaceuticals and agrochemicals. 1,2,3-Triazoles have a wide spectrum of biological activities [13], such as antibacterial [14], herbicidal, fungicidal, antiallergic, and anti-HIV [15] properties. 4-Aryl-1*H*-1,2,3-triazoles have been used as human methionine aminopeptidase (hMetAP2) and indoleamine 2,3-dioxygenase (IDO) inhibitors and are expected to become medicines to treat cancers, AIDS, Alzheimer's disease, tristimania, cataracts, and some other serious diseases [16].

Huisgen 1,3-dipolar cycloaddition of organic azides to alkynes is one of the most important synthetic routes to 1,2,3-triazole derivatives [17], which have been utilized as dyes, photo stabilizers, agrochemicals, and biochemicals [18]. The Cu-catalyzed azide-alkyne cycloaddition (CuACC) reaction has been traditionally implemented with advantages are however the methodologies in which the organic azides are generated in situ from organic halides [19], (three-component azide-alkyne cycloaddition) because hazards derived from their isolation and handling are minimized, time-consuming, and waste-generating additional synthetic steps are avoided. The common organic solvents utilized (e.g., dioxane, toluene, DMF, dichloromethane, and THF) can be replaced by neat water. In this vain, efforts have been recently devoted to develop new catalytic systems, which allow the CuAAC from other azide. Sahu *et al.* reported regioselectivity of vinyl sulfone-based 1,3-dipolar cycloaddition reactions with sugar azides by computational and experimental studies [20]. Wua *et al.* described base-mediated reaction of vinyl bromides with aryl azides: one-pot synthesis of 1,5-disubstituted 1,2,3-triazoles [21]. Li *et al.* described facile one-pot synthesis of 4,5-disubstituted 1,2,3-(*NH*)-triazoles through Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides, terminal acetylenes, and sodium azide [22].

Favi *et al.* reported one-pot copper (II)-catalyzed Aza–Michael addition of trimethylsilyl azide to 1,2-diaza-1,3-dienes and copper(I)-catalyzed 1,3-dipolar cycloaddition of the in situ generated α-azido hydrazones with alkynes [23]. However, alkynes are the most commonly used starting materials that can provide a carbon framework. Murthy *et al.* [24] described one-pot three-component syntheses of triazoles from organic azides and phenylacetylene using sodium ascorbate as a catalyst in

ethanol at room temperature. Reddy *et al.* reported *p*-TsOH-mediated, versatile, and efficient approach for the synthesis of triazolyl-carbazoles from nitrovinylcarbazoles and azide via 1,3-dipolar cycloaddition [25]. Alonso *et al.* described alkenes as azido precursors for the one-pot synthesis of 1,2,3-triazoles catalyzed by copper nanoparticles on activated carbon [26]. Wang *et al.* reported copper-catalyzed synthesis of 4-aryl-1*H*-1,2,3-triazoles from 1,1-dibromoalkenes and sodium azide [27]. Based on the aforementioned literature we have synthesized, the title compounds in a step-wise and one-pot method from azide and acetylenic compounds.

RESULTS AND DISCUSSION

As outlined in Scheme 1, the commercially available oxindole was taken as a starting material, which on reaction with Vilsmeier reagent yielded the corresponing key *β*-haloaldehyde intermediate **2** [28]. This on treatment with alkylating agents such as methyl iodide, ethyl bromide in acetone at room temperature using K_2CO_3 as a base afforded the corresponding *N*-alkylated *β*-haloaldehyde intermediates **3** and **4** [29]. This on reaction with sodium azide in DMSO as a solvent at 20°C for 12 h gave *N*-alkylated *β*-azide aldehyde intermediates 5 and 6 [30].

In order to synthesize the target compounds of triazoles, by using azide with phenyl acetylene in the presence of sodium ascorbate as an additive and copper halide as a catalyst in DMF solvent for 8 h at room temperature resulted in triazoles **7a** albeit in low yield 30%. However, generally, it did not exceed 30% (Table 1, entry 1). When $CuSO_4{\cdot}5H_2O$ was used as a catalyst (Table 1, entry 9), the reaction was proceeded and gave 90% yield at room temperature in 10 min. Unfortunately, the obtained title compounds were very unstable, so these compounds were immediately analyzed by recording NMR, otherwise decomposed. Among all conditions used, $CuSO_4{\cdot}5H_2O$ was found to be the best catalyst and DMF as the best solvent in terms of reaction time and yield of the product formed. Thus, using $CuSO_4{\cdot}5H_2O$-DMF system, we synthesized the title compounds in good to excellent yields. The structures of all these compounds were confirmed by the analytical and spectral data.

As shown in Scheme 2, it was thought of interest to synthesize the title compounds **7a**–**f** by one-pot synthesis. Compounds **8a**–**d** on treatment with sodium azide in DMSO solvent for 12 h at 20°C resulted in the formation of azide intermediate compounds. This reaction mixture was treated with phenyl acetylene, sodium ascorbate as an additive and copper halides as a catalyst in DMF solvent at room temperature for 12–13 h resulted in the

Scheme 1. Synthesis of *N*-alkylated 2-(4-benzyl-1*H*-1,2,3-triazol-1-yl)-1*H*-indole-3-carbaldehydes from indolin-2-one. [Color figure can be viewed at wileyonlinelibrary.com]

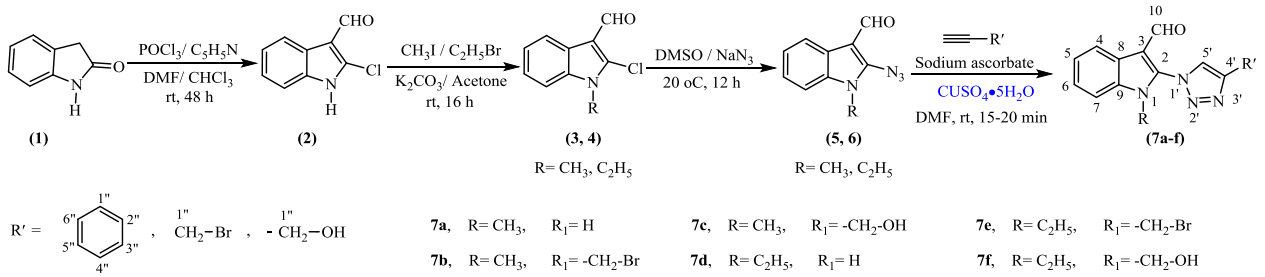
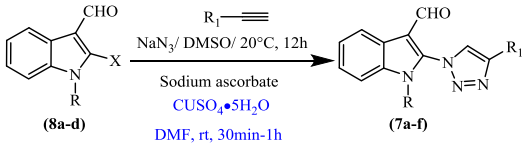


Table 1

Catalyst optimization for the synthesis of triazoles from indolin-2-one.

Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Yield (%)
1	DMF	CuI	rt	8	0
2	DMF	CuBr	rt	6	20
3	DMF	CuCl	rt	5	20
4	DMF	Cu_2O	rt	8	0
5	DMF	$Cu(PPh_3)_2NO_3$	rt	6	0
6	DMF	$Cu(PPh_3)_2Cl$	rt	5	0
7	DMF	$Cu(PPh_3)_2Br$	rt	3	0
8	DMF	$[Cu(Phen)(PPh_3)_2]NO_3$	rt	7	0
9	DMF	$CuSO_4{\cdot}5H_2O$	rt	10–30 min	90
10	DMF	$Cu(AcO)_2$	rt	4	40

Scheme 2. One-pot synthesis of *N*-alkylated 2-(4-benzyl-1*H*-1,2,3-triazol-1-yl)-1*H*-indole-3-crbaldehydes from 1-alkyl-2-halo-1*H*-indole-3-carbaldehyde. [Color figure can be viewed at wileyonlinelibrary.com]



8a: R= CH_3,, X= Cl **8b:** R= CH_3, X= Br **8c:** R= C2H5, X= Cl **8d:** R= C_2H_5, X= Br

7a: R= CH_3, R_1= H **7b:** R= CH_3, R_1= -CH_2-Br **7c:** R= CH_3, R_1= -CH_2-OH

7d: R= C_2H_5, R_1= H **7e:** R= C_2H_5, R_1= -CH_2-Br **7f:** R= C_2H_5, R_1= -CH_2-OH

formation of *N*-alkylated 2-(4-benzyl-1*H*-1,2,3-triazol-1-yl)-1*H*-indole-3-carbaldehyde in low yields 20% (Table 2, entries 1–3).

On further screening of catalyst in DMF (Table 2, entries 4–8), the reaction was failed. When $CuSO_4{\cdot}5H_2O$ was used as a catalyst (Table 2, entry 9), the reaction was achieved in 80% at room temperature for 1–3 h. Among all observed conditions, here also $CuSO_4{\cdot}5H_2O$ was found to be the best catalyst and DMF as the best solvent in terms of reaction time and the yield of product formed. Thus, using $CuSO_4{\cdot}5H_2O$-DMF system, we synthesized the title compounds in good yields.

As shown in Scheme 3, by adopting the method of reference [31], compounds **9**–**13** were synthesized. Reactions were conducted on **14**, **15** with phenyl azide, sodium ascorbate as an additive and $CuSO_4{\cdot}5H_2O$ as a catalyst in DMF solvent for 2–3 h at room temperature to obtain the products in good yields.

As shown in Scheme 4, compounds **22**, **23** were prepared by using the method of reference [32]. Compound **18** on reaction with alkylating agents such as methyl iodide, ethyl bromide gave **19** and **20**, which on further coupling with 4-phenyl triazole **(21)** in the presence of iodosuccinimide as a catalyst and K_2CO_3 as a base at room temperature for 1 h resulted in the formation of compounds **22** and **23** [33]. Preliminary mechanistic investigation was carried out to understand this mechanism at the combination of 3-indolylaldehyde and 4-phenyltriazole by reference [32] and provided in Figure 1.

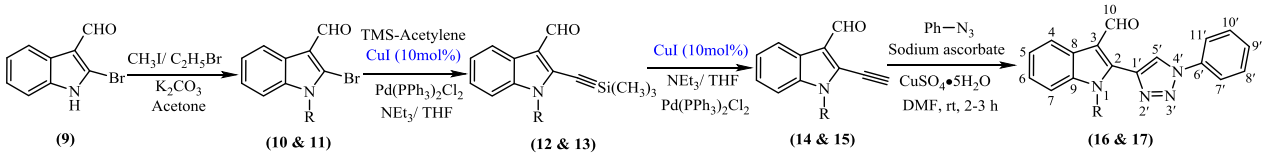
Table 2

Optimization of catalysts for the synthesis of triazoles from 1-alkyl-2-halo-1*H*-indole-3-carbaldehyde.

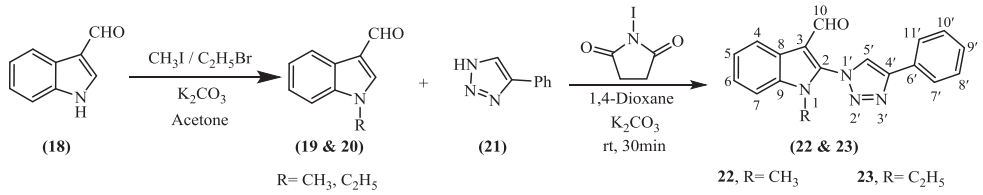
Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Yield (%)
1	DMF	CuI	rt	9	20
2	DMF	CuBr	rt	6	15
3	DMF	CuCl	rt	6	10
4	DMF	Cu_2O	rt	7	0
5	DMF	$Cu(PPh_3)_2NO_3$	rt	10	0
6	DMF	$Cu(PPh_3)_2Cl$	rt	12	0
7	DMF	$Cu(PPh_3)_2Br$	rt	10	0
8	DMF	$[Cu(Phen)(PPh_3)_2]NO_3$	rt	16	0
9	DMF	$CuSO_4{\cdot}5H_2O$	rt	1–3	80
10	DMF	$Cu(AcO)_2$	rt	8	40

The aforementioned step-wise method gave excellent yields when compared with one-pot method by using different azides and acetylenes in short reaction time and yields are good.

Scheme 3. Synthesis of *N*-alkylated 2-(4-benzyl-1*H*-1,2,3-triazol-1-yl)-1*H*-indole-3-carbaldehydes from 2-bromo-1*H*-indole-3-carbaldehyde. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 4. Synthesis of *N*-alkylated 2-(4-benzyl-1*H*-1,2,3-triazol-1-yl)-1*H*-indole-3-carbaldehyde from 1*H*-indole-3-carbaldehyde.



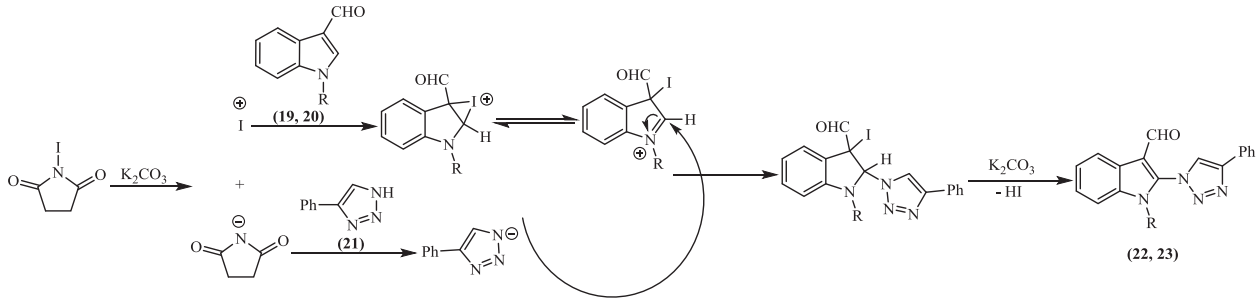


Figure 1. Plausible mechanism for the formation of compounds **22** and **23**.

CONCLUSIONS

In conclusion, we have developed a new efficient method for the synthesis of triazole-linked indole aldehyde by step-wise and one-pot method by Huisgen's 1,3-dipolar cycloaddition of azide and alkynes under click reaction. A series of *N*-alkylated 2-(4-subtituted-1*H*-1,2,3-triazol-1-yl)-1*H*-indole-3-carbaldehydes were prepared in good to excellent yields, using different copper catalysts in DMF solvent. For these reactions, $CuSO_4 \cdot 5H_2O$ was found to be the best catalyst in terms of reaction time, yields of the products and easy work-up procedure.

EXPERIMENTAL

All the commercially available starting materials, reagents, catalysts, and solvents were used without purification unless stated otherwise. All products were purified by silica gel (200–300) column chromatography. Melting points are uncorrected and were determined in open capillary tubes using Guna melting point apparatus. TLC analyses were run on silica gel-G, and visualization was performed using UV lamp or iodine. ^1H and ^{13}C NMR spectra were recorded on Bruker 400 MHz instrument in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard using 400 and 100 MHz, respectively. Mass spectra were recorded on Agilent-LCMS instrument.

General procedure for the title compounds. In a round bottom flask equipped with a magnetic stirring bar, 1.0 mmol of 2-azido-3-carbaldehyde was stirred with 1.0 mmol of phenyl acetylene in DMF. After stirring for 5 min at room temperature, 1.0 mmol of sodium ascorbate and 1.0 mmol of $CuSO_4 \cdot 5H_2O$ were added. The reaction was stirred up to completion of reaction as indicated by the TLC. Crushed ice was added to the crude reaction mass. Then aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate). All the compounds were characterized by the spectral studies and the representative spectra (Compounds **5**, **7b** and **22**) have been provided in the supporting information.

Spectral data for title compounds. ***2-(4-(Bromomethyl)-1H-1,2,3-triazol-1-yl)-1-methyl-1H-indole-3-carbaldehyde (7b).*** Brown solid, yield: 90%, mp: 120–222°C; IR (KBr): 2958, 2861, 2240, 1720, 1582, 1444, 1356, 1243, 805; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.50 (s, 3H, CH_3), 6.58 (s, 2H, Ar–CH_2), 7.14–7.11 (t, J = 7.6 Hz, 4H, Ar–H), 7.65–7.64 (d, J = 6.4 Hz, 1H, Ar–H), 9.94 (s, 1H, Ar–CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.4, 29.7, 108.4, 115.2, 121.1, 122.2, 126.3, 134.5, 152.9, 181.4; MS (positive mode) m/z: 321[M + H]$^+$; *Anal*. Calcd (%) for $C_{13}H_{11}BrN_4O$; C, 48.92; H, 3.47; N, 17.55; found: C, 48.85; H, 3.36; N, 17.45.

2-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)-1-methyl-1H-indole-3-carbaldehyde (7c). White solid, yield: 85%, mp: 100–102°C; IR (KBr): 3058, 2961, 2140, 1710, 1592, 1454, 1366, 1253, 705; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.55(s, 3H, CH_3), 4.25 (s, 1H, OH) 6.48 (s, 2H, Ar–CH_2), 7.26–7.24 (t, J = 9.6 Hz, 4H, Ar–H), 7.63–7.61 (d, J = 8.1 Hz, 1H, Ar–H), 10.1 (s, 1H, Ar–CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.2 29.3, 108.6, 114.5,

122.3, 123.4, 125.4, 133.5, 153.9, 185.4. MS (positive mode) *m*/*z*: 257 $[M + H]^+$; *Anal*. Calcd (%) for $C_{13}H_{12}N_4O_2$; C, 60.93; H, 4.72; N, 21.86; found: C, 60.97; H, 4.70; N, 20.84.

2-(4-(Bromomethyl)-1H-1,2,3-triazol-1-yl)-1-ethyl-1H-indole-3-carbaldehyde (7e). Brown solid, yield: 85%, mp: 110–112°C; IR (KBr): 2988, 2851, 2120, 1715, 1682, 1442, 1356, 1253, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.80–1.78 (t, *J* = 8.4 Hz, 3H, CH_3), 4.30–4.26 (q, 2H, CH_2), 6.55 (s, 2H, Ar–H), 7.14–7.12 (t, *J* = 8.0 Hz, 4H, Ar–H), 7.63–7.62 (d, *J* = 5.6 Hz, 2H, Ar–H), 10.2 (s, 1H, Ar–CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 27.5, 38.5, 109.2, 110.7, 122.1, 123.5, 124.4, 135.6, 153.9, 185.6; MS (positive mode) *m*/*z*: 334 $[M + H]^+$; *Anal*. Calcd (%) for $C_{14}H_{13}BrN_4O$; C, 50.47; H, 3.93; N, 16.82; found: C, 50.43; H, 3.95; N, 16.84.

1-Ethyl-2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-1H-indole-3-carbaldehyde (7f). White solid, yield: 80%, mp: 93–95°C; IR (KBr): 3026, 2970, 2150, 1715, 1582, 1454, 1367, 1253, 705; ^{1}H NMR (400 MHz, $CDCl_3$): 1.80–1.78 (t, *J* = 8.4 Hz, 3H, CH_3), 4.30–4.26 (q, 2H, CH_2), 4.15 (s, 1H, OH) 6.15 (s, 2H, Ar–CH_2), 7.15–7.13 (t, *J* = 8.2,Hz, 4H, Ar–H), 7.53–7.51 (d, *J* = 8.1 Hz, 1H, Ar–H), 10.3 (s, 1H, Ar–CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 27.3, 39.5, 108.3, 114.1, 122.5, 123.4, 125.5, 133.2, 153.8, 186.4; MS (positive mode) *m*/*z*: 271 $[M + H]^+$; *Anal*. Calcd (%) for $C_{14}H_{14}N_4O_2$; C, 62.21; H, 5.22; N, 20.73; found: C, 62.15; H, 5.25; N, 20.76.

1-Methyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-1H-indole-3-carbaldehyde (22). Pale yellow solid, yield: 90%, mp: 148–150°C; IR (KBr): 3095, 3051, 1660, 1610, 1561, 1479, 1369, 1228, 1128, 1030, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.74 (s, 3H, CH_3), 7.53–7.26 (m, 6H, Ar–H), 7.97–795 (d, *J* = 7.6 Hz, 2H, Ar–H), 8.27 (s, 1H, Ar–H), 8.40–8.38 (d, *J* = 8.0 Hz, 1H, Ar–H) 9.89 (s, 1H, Ar–CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.6, 110.3, 110.9, 122.3, 122.6, 124.3,125.5, 126.0, 128.3, 129.1, 129.1, 129.2, 132.1, 135.2, 137.3, 148.2, 183.1; MS (positive mode) *m*/*z*: 303 $[M + H]^+$; *Anal*. Calcd (%) for $C_{18}H_{14}N_4O$; C, 71.51; H, 4.67; N, 18.53; found: C, 71.48; H, 4.61; N, 18.45.

1-Ethyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-1H-indole-3-carbaldehyde (23). Pale yellow solid, yield: 85%, mp: 130–132°C; IR (KBr): 3032, 3010, 1651, 1601, 1542, 1469, 1351, 1215, 1120, 1010, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50–1.48 (t, *J* = 8.2 Hz, 3H, CH_3), δ 4.44–4.38 (q, 2H, CH_2), 7.51–7.22 (m, 6H, Ar–H), 7.91–789 (d, *J* = 8.4 Hz, 2H, Ar–H), 8.23 (s, 1H, Ar–H), 8.38–8.36 (d, *J* = 8.3 Hz, 1H, Ar–H) 10.2 (s, 1H, Ar–CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 37.5, 109.3, 110.9, 121.3, 122.6, 123.2, 125.3, 125.1, 127.3, 128.1, 129.4, 129.5, 132.5, 134.2, 136.3, 147.2, 185.1; MS (positive mode) *m*/*z*: 317 $[M + H]^+$; *Anal*. Calcd (%) for $C_{19}H_{16}N_4O$; C, 72.13; H, 5.10; N, 17.71; found: C, 72.10; H, 5.11; N, 17.73.

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CONFLICTS OF INTEREST

We state we have no conflicts of interest.

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