Canadian Chemical Transactions Year 2016 | Volume 4 | Issue 2 | Page 255-266

Research Article

DOI:10.13179/canchemtrans.2016.04.02.0318

Synthesis of [3, 3':3', 3''-terindolin]-2'-ones by using Recyclable, Magnetically Separable Nano Copper Ferrite Catalyst and their Antibacterial Studies

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***Received:** May 4, 2016* ***Revised:** May 28, 2016* ***Accepted:** June 8, 2016* ***Published:** June 16, 2016*

Abstract: An efficient, simple, ecofriendly and cost effective method has been developed for the synthesis of [3, 3':3', 3"-terindolin]-2'-one derivatives (3a-3l) by one pot reaction of indoline-2, 3-diones with 1H-indoles using nano copper ferrite catalyst (20 mol%) in water with excellent yields (89-99%). The Indoles with strong releasing groups gave high yields (3d, 3h and 3l) in this reaction. The most important feature of this protocol is the use of recyclable catalyst. These compounds were screened for anti bacterial activity. Compounds 3c, 3f and 3k have shown potential antibacterial activity.

Keywords: Bis indole, Nano copper ferrite Catalyst, Recyclable Catalyst, Antibacterial activity.

1. INTRODUCTION

Multicomponent reactions (MCR) are novel, economically viable, less time consuming approaches for the synthesis of bio active heterocyclic compounds from simple starting materials, without isolation of intermediates [1-5]. The significance of MCRs in organic synthesis and medicinal chemistry is ever increasing. Isatin is the lead molecule for designing potential bio-active agents such as anti-viral [6], anti- tumor [7], anti-fungal [8], anti HIV [9] and anti-convulsants [10]. Indoles and its derivatives are found in nature and exhibit physiological properties [11]. In particular 3, 3-diaryloxindole is frequently found in clinical drugs and biological active compounds. Bis (indolyl) methanes isolated from natural sources, like vibrindole, have shown promising biological activity. Generally 3, 3-di (indolyl) indolin-2-ones, also called as bis indoles, are prepared by coupling of isatin with indoles under acidic conditions [12]. B V Subba Reddy et al reported the synthesis of Bis indoles by using Iodine catalyst [13]. However, only a few methodologies have been reported for the synthesis of 3, 3-di (indolyl) indolin-2-ones [14-18]. Hence the development of simple and efficient method is desirable for the synthesis of [3, 3':3', 3"-terindolin]-2'-one derivatives.

In recent years, magnetic nano particles have emerged as a useful group of heterogeneous catalysts. Separation of magnetic nano particles is simple and an attractive alternative to filtration as it prevents loss of catalyst and enhances reusability. The use of low-cost and readily available species as catalyst is crucial for ascertaining economic feasibility of the chemical processes. Copper ferrite nanoparticles (CuFeNPS) have the advantages of recyclability, easy work-up, and cleaner reaction profiles apart from the lack of necessity for external ligands thereby minimizing the organic waste generation when compared to the conventional catalytic systems. Moreover, they have also shown good stability in various organic transformations [19]. The use of water as a green solvent for organic synthesis has been attracting considerable attention [20]. In the present work, a novel green synthetic method is used to synthesize the [3, 3':3', 3"-terindolin]-2'-one derivatives by using isatin, indoles and recyclable nano copper ferrite catalyst. These compounds are screened for antibacterial studies.

2. MATERIALS AND METHODS

2.1. Experimental

All the chemicals were purchased from Sigma Aldrich with purity not less than 99.9%. Analytical Thin Layer Chromatography (TLC) was carried out by using silica gel 60 F254 pre-coated plates. Visualization was accomplished with UV lamp of I_2 stain. All the products were characterized by their NMR and Mass spectra. ^{1}H NMR and ^{13}C NMR were recorded on 300 MHz and 75 MHz, in $CDCl_3$/DMSO, and the chemical shifts were reported in parts per million (ppm, δ) downfield from the Tetramethyl silane (TMS).

2.2 General experimental procedure for synthesis of bis-indoles

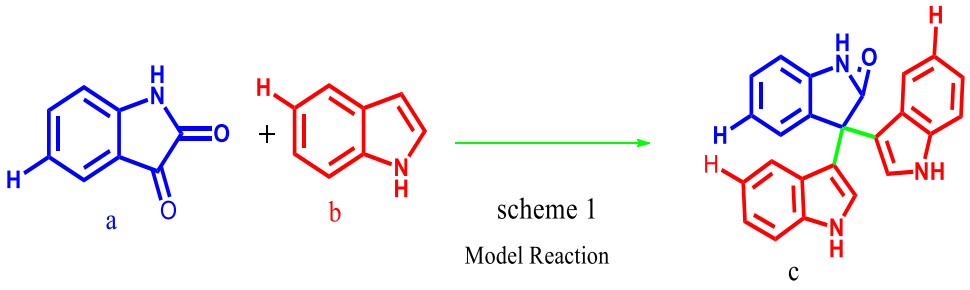
Isatin(1 mmol), indole (2 mmol), 20 mol% CuFeNPS and water as solvent were taken in a 100 ml round bottam flask. The reaction mixture was stirred for 30 min, at 110 ^{o}C. The progress of the reaction was monitored by TLC. After the completion of the reaction the catalyst was separated by using external magnet and cooled reaction mixture was filterd and the obtained solid product is washed with ethyl acetate before drying over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by silica-gel chromatography to give the desired bis indoles in excellent yields. The identity and purity of the products were confirmed by ^{1}H, ^{13}C NMR, and mass spectra.

3. RESULTS AND DISCUSSIONS

3.1. Chemistry

Initially a model reaction is conducted at room temperature using different solvents and different mol% of catalyst for synthesis of Bis indoles to investigate the feasibility of the reaction.

Isatin and Indole were taken in different solvents, stirred for 1hr, 2hr, and 3hr duration without catalyst at room temperature. It is observed that very low yield (<10, Table1, entry 1-5) of products is obtained even after 3 hours of stirring. There was a slight increase in yield (10% to 50%, table 1, entry 6-10), when the reaction mixture is added with 5 mol% nano copper ferrite catalyst even on stirring for just 1 hour at 100^{0}C. It was observed that yield (48%) obtained was much better in water solvent at the same reaction conditions. On increasing the catalyst to 10 and 15 mol%, there was increase in yield up to 68%



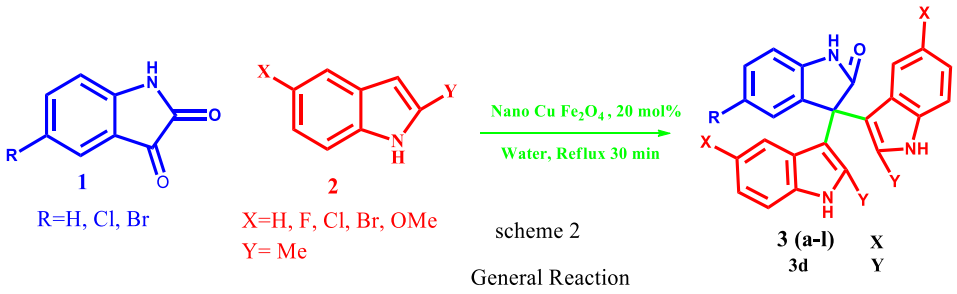
Scheme 1. Synthesis of [3, 3': 3', 3"-terindolin]-2'-one

and 85% respectively at 100^0C. Further increasing the catalyst to 20 mol% increased the yield to 93% (table 1, entry 12), in 30 min at 100^0C. All the results are summarized in table 1. No change was observed on further enhancing the catalyst mol% or time of stirring.

Table 1. Optimization of reaction conditions

S. No	Solvent	Catalyst	Time	Temp	Yield
1	--	--	3 hr	RT	**--**
2	ethanol	--	3hr	RT	**10<**
3	DMSO	--	3hr	RT	**10<**
4	CH_3CN	--	3hr	RT	**10<**
5	Water	--	3hr	RT	**10<**
6	ethanol	5 (mol %)	1 hr	100	**18**
7	DMSO	5 (mol %)	1hr	100	**21**
8	CH_3CN	5 (mol %)	1 hr	100	**22**
9	Water	5 (mol %)	1 hr	100	**48**
10	Water	10 (mol %)	1 hr	100	**68**
11	Water	15 (mol %)	30 min	100	**85**
12	Water	20 (mol %)	30 min	100	**93**
13	Water	20 (mol %)	1hr	100	**93**
14	Water	25 (mol %)	30 min	100	**93**
15	Water	30 (mol %)	30 min	100	**93**

To further explore the scope of this reaction, different indoline-2, 3-diones, 1H-indoles were made use of in an attempt to synthesize bis indoles (scheme2) and the results are summarized in table 3. As illustrated in table 3, the method showed good tolerance when isatin is made to react with commercially available Indoles with substituent groups/functional groups that include methyl, methoxy, fluorine, chlorine and bromine. Accordingly, the desired [3, 3':3', 3"-terindolin]-2'-one derivatives were obtained in good yields by this method than previously reported methods. Substituted indoles afforded greater yields than simple indoles. Among substituted ones, indoles having strong electron releasing groups such as -OCH_3 &-CH_3 gave excellent yields. Compounds 3l, 3h, and 3d were formed in 98-99% yields. Indoles with weak electron releasing groups/atoms also gave good yields, but less than that of the former case. It is noteworthy to mention that this protocol affords good to excellent yields of [3, 3': 3', 3"-terindolin]-2'-one derivatives. Indoles with electron withdrawing groups were tried unsuccessfully. During trial runs, almost no variation in yield% was observed on replacing the hydrogen with Cl or Br on isatin moiety. The structures of synthesized Bis indoles were confirmed by H^1 NMR, C^{13} NMR and Mass spectral analysis.



Scheme 2. Synthesis of [3, 3':3', 3"-terindolin]-2'-one derivatives

The plausible mechanism for the formation of [3, 3': 3', 3"-terindolin]-2'-one from indoline-2, 3-dione and 1H-indole using CuFeNPS is shown in figure 1. The reaction may proceed through the formation of highly reactive (Z)-3-(3H-indol-3-ylidene) indolin-2-one. The efforts to isolate intermediates were not successful.

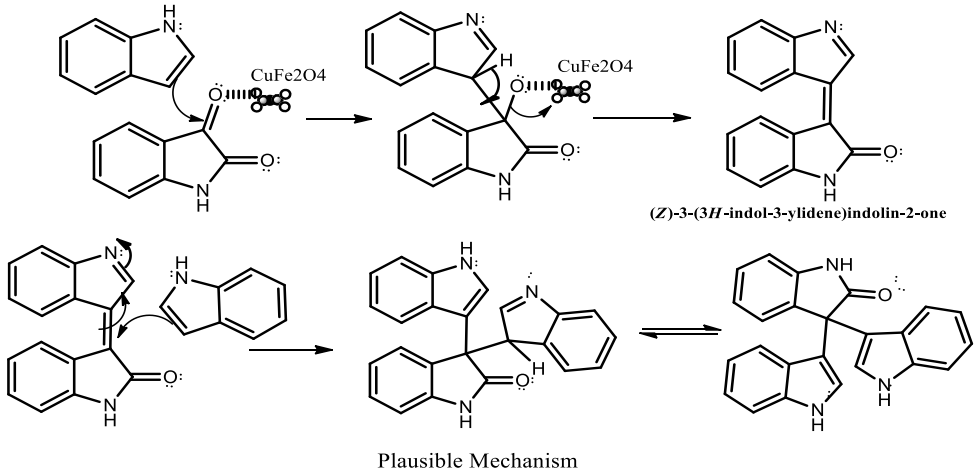


Figure 1. Plausible Reaction pathway for synthesis of [3, 3': 3', 3"-terindolin]-2'-ones

Table 2. $CuFe_2O_4$catalysed synthesis of [3, 3':3', 3"-terindolin]-2'-one derivatives

Entry	Isatin (R =)	Indole(X=)	Time(Mins)	Yield (%)
3a	H	H	30	93
3b	H	F	30	92
3c	H	Br	30	96
3d	H	2-Me	30	98
3e	Cl	F	30	90
3f	Cl	Cl	30	91
3g	Cl	Br	30	89
3h	Cl	OMe	30	99
3i	Br	H	30	89
3j	Br	F	30	90
3k	Br	Br	30	87
3l	Br	OMe	30	99

Table 3. Yields of the product with various cycles of the catalyst.

Entry	Reaction Cycle	Yield (%)
1	1^{st} cycle (Fresh run)	93
2	2^{nd} cycle	92
3	3^{rd} cycle	90
4	4^{th} cycle	90
5	5^{th} cycle	89
6	6^{th} cycle	86
7	7^{th} cycle	84
8	8^{th} cycle	56

The reusability of the CuFeNPS is one of the most important advantages of this protocol that makes it useful for practical commercial applications. Thus in this process the catalyst was separated by using external magnet and washed with ether and dried. Interestingly the recovered catalyst could be reused up to 7 cycles under the specified conditions. The yields obtained in seven cycles with simple indoles are as shown in Table 3.

3.3 Spectral data

3a) [3, 3': 3', 3''-terindolin]-2'-one

White solid. ; Mp: 332-335 ˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.80-7.06(m, 8H), 7.19(t, J= 7.55 & 16.24Hz, 1H), 7.27-7.35(m, 5H), 10.00(s, 1H), 10.11(s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 179.3, 137.5, 140.6, 137.0, 127.9, 126.5, 126.1, 125.3, 124.8, 121.5, 121.2, 118.9, 114.2, 112.0, 111.3, 53.5. ESI-MS: m/z = 364 $(M+H)^+$.

3b) 5, 5''-difluoro-[3, 3':3', 3''-terindolin]-2'-one

White solid. ; Mp: 298-300˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.78(td, J= 8.87 & 2.45Hz, 2H), 6.91-7.02(m, 6H), 7.18-7.29 (m, 4H), 10.18(s, 1H), 10.42(s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.68, 157.70, 154 .63, 140.92, 133.71, 133.37, 127.51, 125.81, 125.56, 124.46, 121.27, 114.08, 114.02, 111.98, 111.85, 109.55, 109.15, 108.80, 105.27, 104.95, 52.14. ESI-MS: m/z = 400 $(M+H)^+$.

3c) 5, 5''-dibromo-[3, 3':3', 3''-terindolin]-2'-one

Light brown solid. ; Mp: >350 ˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.91-7.25(m, 9H), 7.34-7.47(m, 4H), 9.99(s, 1H), 10.23(s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 179.05, 140.43, 135.42, 133.46, 127.64, 127.02, 125.48, 124.62, 123.73, 122.75, 121.64, 113.69, 112.75, 111.59, 109.72, 59.83. ESI-MS: m/z = 399 $(M+H)^+$.

3d) 2, 2''-dimethyl-[3, 3':3', 3''-terindolin]-2'-one

Pale pink solid. ; Mp: 335-337˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.01 (s, 3H), 2.16(s, 3H), 6.48(d, J= 8.12Hz, 1H), 6.65(q, J= 7.71Hz, 2H), 6.80-6.97(m, 5H), 7.15-7.25(m, 4H), 9.97-10.01(m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 179.49, 140.82, 135.38, 134.73, 133.80, 131.72, 127.58, 126.96, 125.23, 120.88, 119.38, 119.24, 117.65, 110.25, 109.91, 109.16, 52.40, 12.96. ESI-MS: m/z = 392 $(M+H)^+$.

3e) 5'-chloro-5, 5''-difluoro-[3, 3':3', 3''-terindolin]-2'-one

Light yellow solid. ; Mp: >350 ˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.77-7.00(m, 7H), 7.13-7.33(m, 4H), 10.50(s, 1H), 10.73(s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): 177.9, 139.2, 136.1, 135.6, 126.5, 125.1, 124.7, 123.9, 123.5, 120.1, 119.8, 117.5, 112.8, 110.6, 110.0, 52.1. ESI-MS: m/z = 434 $(M+H)^+$.

3f) 5, 5', 5''-trichloro-[3, 3':3', 3''-terindolin]-2'-one

Pale pink solid. ; Mp: 325-327 ˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.91-7.11(m, 6H), 7.19-7.34(m, 5H), 10.46(s, 1H), 10.70(s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.24, 139.75, 135.26, 127.62,

126.16, 125.99, 125.67, 124.49, 123.39, 121.06, 119.46, 113.03, 112.67, 110.90, 52.33. ESI-MS: m/z = 467 $(M+H)^+$.

3g) 5, 5''-dibromo-5'-chloro-[3, 3':3', 3''-terindolin]-2'-one

White color solid. ; Mp: >350 ˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.89-7.29(m, 9H), 7.48-7.55(m, 2H), 10.39 (s, 1H), 10.58(s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 179.9, 153.1, 141.6, 135.1, 132.7, 127.9, 126.6, 125.6, 125.4, 121.9, 114.2, 112.2, 111.1, 109.9, 103.7, 53.2. ESI-MS: m/z = 556 $(M+H)^+$.

3h) 5'-chloro-5, 5''-dimethoxy-[3, 3':3', 3''-terindolin]-2'-one

Grey color solid. ; Mp: 250-252˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.611(s, 6H), 6.72-6.97(m, 4H), 6.94-6.97(s, 3H), 7.15-7.25 (m, 4H), 9.82(s, 2H), 10.08(s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.31, 152.78, 147.62, 142.16, 131.51, 128.56, 126.83, 126.26, 123.57, 123.19, 118.36, 113.74, 113.39, 111.64, 111.30, 110.61, 100.12, 54.90, 30.84. ESI-MS: m/z = 458 $(M+H)^+$.

3i) 5'-bromo-[3, 3':3', 3''-terindolin]-2'-one

Light yellow solid. ; Mp: 345-347˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.80-7.06(m, 7H), 7.15-7.36(m, 6H), 10.43(s, 1H), 10.56(s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.49, 139.77, 136.72, 136.21, 127.15, 125.67, 125.27, 124.51, 124.06, 120.70, 120.37, 118.07, 113.37, 111.22, 110.56, 52.73. ESI-MS: m/z = 443 $(M+H)^+$.

3j) 5'-bromo-5, 5''-difluoro-[3, 3':3', 3''-terindolin]-2'-one

Pale pink solid. ; Mp: >350 ˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.93-7.19(m, 6H), 7.22-7.32(m, 5H), 10.14(s, 1H), 10.41(s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.4, 157.4, 151.9, 146.7, 141.3, 130.6, 127.7, 125.9, 125.4, 122.7, 122.3, 117.5, 112.9, 112.5, 110.8, 110.4, 109.7, 99.2, 54.0. ESI-MS: m/z = 479 $(M+H)^+$.

3k) 5, 5', 5''-tribromo-[3, 3':3', 3''-terindolin]-2'-one

White solid. ; Mp: >350 ˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.88-7.09(m, 3H), 7.12-7.46(m, 8H), 10.55(s, 1H), 10.81(s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.6, 139.9, 134.5, 133.9, 132.9, 130.8, 126.7, 126.3, 126.1, 124.3, 120.0, 118.5, 118.4, 116.8, 109.4, 109.0, 108.3, 51.5. ESI-MS: m/z = 600 $(M+H)^+$.

3l) 5'-bromo-5, 5''-dimethoxy-[3, 3':3', 3''-terindolin]-2'-one

Wine yellow solid. ; Mp: 333-335 ˚C: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.01-2.03(m, 3H), 2.18(s, 3H), 6.49(d, J=8.12 Hz, 1H), 6.69 (t, J=7.55Hz, 2H), 6.85-6.96(m, 4H), 7.15-7.27(m, 4H), 9.98(d, 2H), 10.11(s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 179.9, 153.1, 141.7, 135.1, 132.7, 127.9, 126.6, 125.7, 125.4, 121.9, 114.3, 112.2, 111.2, 110.0, 103.7, 55.7, 53.3. ESI-MS: m/z = 503 $(M+H)^+$.

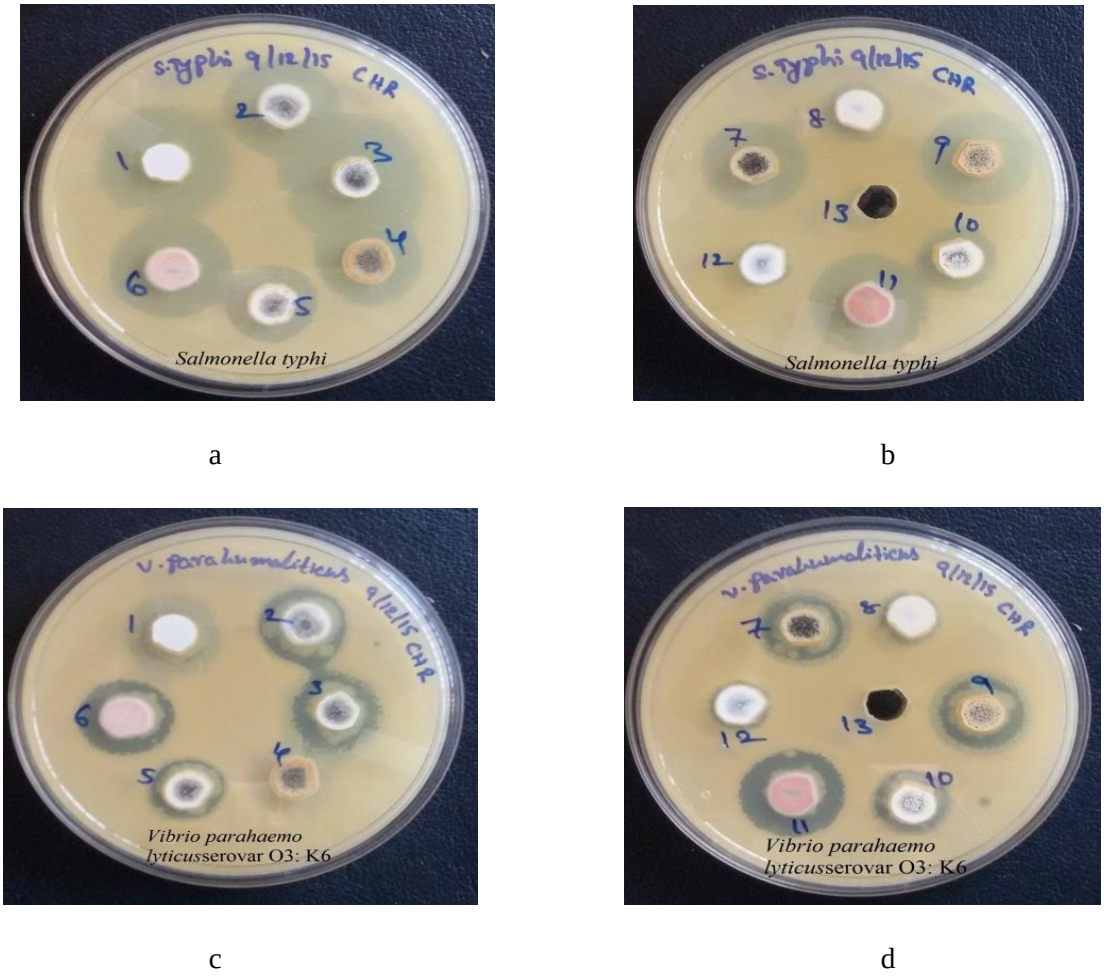
Table 4. Growth inhibition zones (in mm) against human pathogenic bacteria

Code	Compound Solubilized in	Volume of sample tested	Growth inhibition zones (in mm) against human pathogenic bacteria									
			Pseudomonas aeruginosa	*Streptococcus pneumoniae*	*Shigella sonnei*	*Shigella dysenteriae* type 5	*Shigella flexneri* type 2a	*Salmonella typhi*	*Vibrio parahaemolyticus* serovar O3: K6	*Vibrio cholera*	Enterotoxigenic *E.coli* serotype O115	*Salmonella enterica* serovar Typhimurium
3a	DMSO	100 µl	-	16	-	16	18	24	16	-	-	-
3b	DMSO	100 µl	14	20	16	16	18	22	16	18	14	-
3c	DMSO	100 µl	16	16	16	14	18	28	18	18	14	-
3d	DMSO	100 µl	-	-	-	-	16	20	-	-	-	-
3e	DMSO	100 µl	-	15	-	12	14	18	14	12	-	-
3f	DMSO	100 µl	16	20	14	16	18	22	18	18	14	-
3g	DMSO	100 µl	12	14	12	14	14	20	16	18	12	-
3h	DMSO	100 µl	-	-	-	-	-	12	12	12	-	-
3i	DMSO	100 µl	14	16	14	16	14	22	18	20	14	-
3j	DMSO	100 µl	-	12	12	11	-	18	14	16	-	-
3k	DMSO	100 µl	16	18	16	16	18	24	20	20	16	-
3l	DMSO	100 µl	-	-	-	-	-	-	-	12	-	-

3.4 Biology

Antibacterial activity

Antibacterial activity assay was performed by Kirby-Bauer well diffusion method. Antibacterial activity of synthesized compounds were screened against 10 human pathogenic bacteria *Pseudomonas aeruginosa* MTCC3216, *Streptococcus pneumonia* MTCC655, *Shigella sonnei* NK4010, *Shigella dysenteriae* type 5NK2440, *Shigella flexneri* type 2a503004, *Salmonella typhi* MTCC733, *Vibrio parahaemolyticus*serovar O3:K6K5030, *Vibrio cholera* MTCC3905, *Enterotoxigenic E. coli serotype* O1151571, *Salmonella entericaserovar Typhimurium* B12101 as the test microorganisms. All the compounds showed good activity with growth inhibition range of 11mm to 28mm against human pathogenic bacteria. Compounds 3c, 3f and 3k have shown potential activity (Figure 2) against the human pathogenic bacteria and the results are summarized in table 4.



a b

c d

Figure 2. *Antibacterial activity* a) *Salmonella typhi* (compounds 3a to 3f). b) *Salmonella typhi* (compounds 3g to 3l). c) *Vibrio paraha emolyticus*serovar O3: K6 (compounds 3a to 3f). d) *Vibrio parahaemolyticus*serovar O3: K6 (compounds 3g to 3l).

4. CONCLUSION

In conclusion, we have described a novel, efficient, multi-component one pot green synthetic method using nano copper ferrite catalyst and water as solvent. The novelty and synthetic utility of this method is demonstrated in the efficient synthesis of [3, 3': 3', 3"-terindolin]-2'-one derivatives. The advantages of this method include its simplicity of operation, cleaner reaction, and good to excellent yields. Further, the purification of the product is simple involving filtration. The catalyst is easily separated by using external magnet and is reusable up to seven cycles. Furthermore, the compounds are screened for their antibacterial activity against human pathogenic bacteria. Compounds 3c, 3f and 3k have shown potential antibacterial activity.

ACKNOWLEDGEMENT

The corresponding author is grateful to *CSIR*, New Delhi for supporting through fellowship (JRF&SRF) & Department of Engineering chemistry, AUCE (A), Andhra University, Visakhapatnam for providing general lab facilities. The corresponding author is also grateful to *Prof. B V Rao* and *Dr. M K Kumar* for their valuable & constant support.

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The authors declare no conflict of interest