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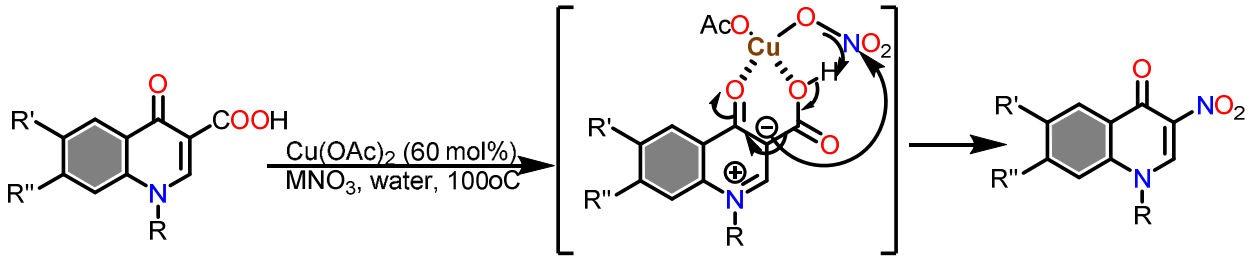
Chandra S. Azad[a], Vishal M. Balaramnavar[b], Imran A. Khan[a], Pawan K.Doharey[c], Jitendra K. Saxena[c], Anil K. Saxena[a]*



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Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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An efficient, cost effective and green methodology for *ipso* nitration in the synthesis of 3-nitro derivative of 3-carboxy 4-quinolones has been developed by the quantitative use of copper acetate and silver nitrate in water. The observed regioselectivity of nitration is explained by the DFT calculations. Three of these compounds with IC_{50} values (2.9-3.4 μmol) against *Brugia malayi* thymidylate kinase may be good antifilarial agents as also evidenced by molecular docking studies.

Introduction

Quinolones belong to a comparatively large, growing and most fascinating group of antibacterial drugs with major influence on antimicrobial chemotherapy.[1] These molecules are of importance because of their high potency, broad spectrum of activity and low prevalence of side-effects. Introduction of fluorine atom at position **6** of quinolone led to the discovery of novel class of broad spectrum fluoroquinolone including the first one-Norfloxacin (**1**).[2] The nitro-heterocycles have been reported as potent antibacterial, antiprotozoal and antifungal agents. The exploration of therapeutical aspects of the prototypes nitrofuran, nitroimidazole and nitropyrroles using the stat of art medicinal chemistry led to the discovery of nitrofurantoin (**2**), metronidazole (**3**) and pyrrolnitrin (**4**) respectively .[3] Hai-Hong Li *et al* has also shown that 3-nitro quinolone **5** is the potent inhibitor of epidermal growth factor receptor (EGFR) (Figure **1**).[4] Other 3-nitro quinolones derivatives have been also screened for their antihistaminic, antiprotozoal and antimalarial activities.[5-7] The adaptability of the nitro compounds in the medicinal chemistry is basically owing to their easy transformation into a variety of assorted functionalities (Figure **2**).[8] Thus in search of privileged scaffold in the drug discovery, we focused our attention towards the synthesis of some novel 3-nitro or 3-amino derivatives of chloro, fluoro quinolones.

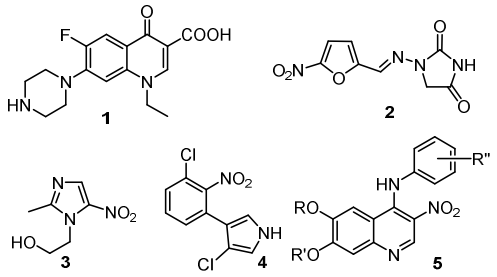


Figure 1. Some biological active nitro compounds.

Many methods have been developed for the synthesis of 3-nitro quinolones (**13):** (a) decarboxylation of **12** followed by regioselective nitration at position 3; [9,10] (b) treating isatoic anhydride with esters of 2-nitro carboxylic acid with opening of oxazine ring followed by its cyclization to 2-hydroxy 3-nitroquinolone;[11] (c) treatment of nitroacetophenone with triethylorthoformate and amine followed by

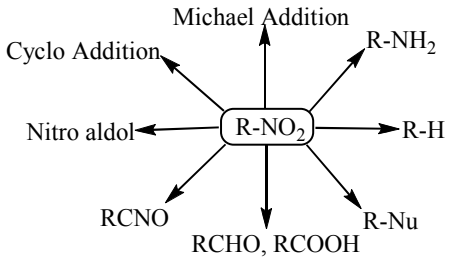
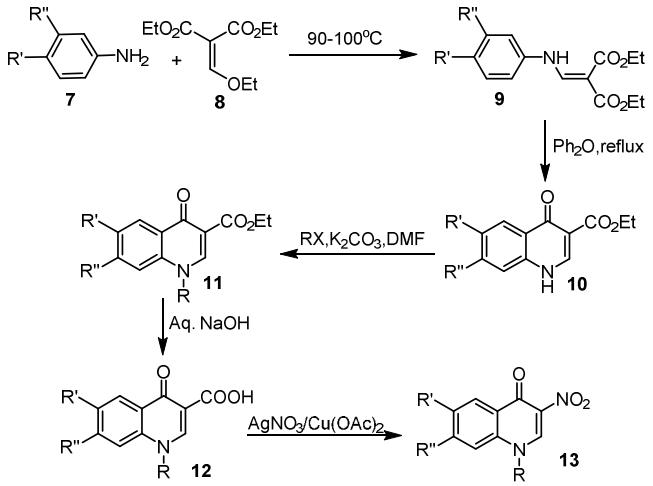


Figure 2. Schematic representation of possible conversions for nitro into variety of functional group.

cyclization at room temperature with DBU;[12] (d) *in situ* or separate preparation of metazonic acid (oxime of 2-nitro acetaldehyde) followed by its treatment with isatine or antharanilic acid and subsequent acetic anhydride assisted thermal cyclization.[13] Although some of these methods are benign, they suffer from practical limitations such as harsh reaction conditions, multistep synthetic processes, problematic starting materials and poor yields. A contemporary one-pot synthesis of 1-alkyl-7-chloro-6-flouro-3-nitro-1,4-dihydro-4-quinolones is attained via nitro-decarboxylation of the respective 4-oxo-1,4-dihydroquinoline-3-carboxylic acid precursor with the help of fuming nitric acid.[14] This novel discovery not only afforded a new route to the synthesis of this class of compounds, but also had the benefits of wide scope of applications. However, this methodology required excess of expensive fuming nitric acid and a special breathing apparatus. In this methodology only two examples have been explored. When we tried to synthesis the 3-nitroquinole by the routine method using the metazonic acid and substituted antharanilic acid, [15] we obtained very poor yield, then we tried the decarboxylation-nitration using the reported method and we got satisfactory yield. However this methodology involved fuming nitric acid, so in continuation of developing new chemical methodologies,[16] it appeared of interest to develop an environmental benign *ipso* nitration methodology devoid of fuming nitric acid. The electrophilic nitration, one of the most extensively studied organic reaction, resulted a mixture of isomeric nitrated products.[17] Since the routine nitrating agents are also good oxidants, the nitrated compounds are often accompanied by oxidation products with excessive acid waste streams and thus add to expenses in the isolation of pure nitrated products. In several methods use of Lewis acid in high stoichiometry followed by aqueous quenching leads in liberation of large amounts of strongly acidic by-products.[18] To overcome these problems, alternative methods for the nitration have been reported in literature. Some of these methods include use of $NaNO_3$/HCl with catalytic $La(NO_3)_3$[19a] $Mg(HSO_4)_2$ or $NaHSO_4 \cdot H_2O$ and $NaNO_3$/wet SiO_2,[19b] montmorillonite KSF/$Bi(NO_3)_3$,[19c] $NaNO_2$/silica sulfuric acid,[19d] $Mg(NO_3)_2 \cdot 6H_2O$/ Alumina Sulphuric acid,[19e] $Cu(NO_3)_2$/clay,[19e] $AgNO_3$/NBS [19f] and $Fe(NO_3)_3 \cdot 9H_2O$/ionic liquid [19g]. Other methods for example reaction of metal nitrate/clay combinations activated by acetic anhydride,[19h] zirconylnitrate,[19i] p-toluenesulfonic acid/$Ni(NO_3)_3$,[19j] $Ca(NO_3)_2$, acetic acid in microwave[19k] and nitration of phenols with *tert*-butyl nitrite [19l] have also been developed. Recently many methods having C-H bond activation with nitration are drawing attention. The *ipso* nitration specially decarboxylative nitration appeared to be an important synthetic methodologies in the synthesis of nitro compounds in high regioselectivity.[20] Therefore, the development of mild and regioselective *ipso* nitration methods with minimal or non-environmental hazardous by-products is of significant interest. Hence a mild, cost effective and environmental benign method for the synthesis of 3-nitro quinolone has been developed an applied to a number of substrates to extend its scope in terms of synthetic and medicinal utility. The results of this study are reported in this manuscript.

Results and Discussion

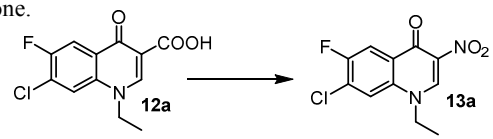
The key substrate 6,7-di halo quinolone -3–carboxylate (**12**) was synthesized by condensing halogenated aniline 7 with diethyl 2-(ethoxymethylene) malonate (EMME, **8**) followed by the thermal cyclisation of the condensed product **9** thus obtained in diphenyl ether to give quinolone ester **10**. The N alkylation of **10** with K_2CO_3 in DMF followed by hydrolysis by aqueous NaOH of the N-alkylated derivative **11** yielded the required key substrate 3-carboxylic acid **12** (Scheme **1**).[21]



Scheme 1. Synthesis of 3-nitro quinolone by silver nitrate and copper acetate mixture.

This key substrate was used for the environment benign nitration by different methods (Table **1**). The investigation started with the use of metal nitrates with acid combination and these methods led to the formation of products in good yield, but methodology required use of high stoichiometric ratio of acids (Table **1**, entry **1-7**).[22] The combination of sulphuric acid with other acids also led to the formation of products with same problem of waste products arises (Table **1**, entry **8-12**).[23] The others reported mild methods for nitration were also tried but the methodologies were limited to the use of non-green approaches (Table **1**, entry **13-15**).[24] The stabilization of β-keto-esters/acids by metals and a new study by L. Zhang *et al.* fortified us to use metal as a catalyst in the reaction medium. [25] The cost effective metals like copper and magnesium were of the first choice. Initially, the effect of metal nitrating agent, catalyst, and solvent was studied under open atmosphere at 100°C and reaction time (24 h), using **12a (R'= F, R" = Cl; R = Et)** as a model substrate (Table **2**).

Table 1. Effect of nitrating reagents on the synthesis of 3-nitro quinolone.



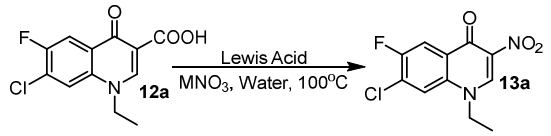
Entry	Nitrating Mixture	Yield (%)[a]	Reaction Time (h.)
1	$Al(NO_3)_3/CH_3COOH$[b]	60	20

2	$Fe(NO_3)_3/CH_3COOH$[b]	54	20
3	$Zn(NO_3)_2/CH_3COOH$[b]	52	20
4	$Mg(NO_3)_2/CH_3COOH$[b]	61	20
5	$Ca(NO_3)_2/CH_3COOH$[b]	56	20
6	$CsNO_3/CH_3COOH$[b]	59	20
7	$Cu(NO_3)_2/CH_3COOH$[b]	71	20
8	HNO_3+PPA[c]	40	15
9	HNO_3+HClO_4[c]	45	15
10	HNO_3+Triflic Acid[c]	62	15
11	HNO_3+CH_3COOH[c]	35	15
12	$HNO_3+H_2SO_4$[c]	82	8.5
13	$TFAA/EtNH_2/HNO_3$[d]	79	22
14	t-BuONO/TEMPO/ACN[d]	82	20
15	$AgNO_3$/TMSCl/DCM (rt)[d]	77	48
16	*tert*-butyl nitrite/ACN/rt[d]	52	18

[a] Isolated yield. [b]Reagent **12a**, (1mmol) nitrate salt (1.5 mmol) and 10 ml/mmol CH_3COOH at 100°C. [c]12a (1mmol) in 10 ml of nitrating mixture (1:2) 120°C. [d]Reactions for 13-16 were performed according to reported methods in references 24a, 24d, 24c and 24f respectively.

Metal catalysts were first screened using $AgNO_3$ as a nitrating agent and water as a solvent. The 60 mol % $Cu(OAc)_2$ was found to be essential for an efficient conversion producing **13a** in 92% yield within 20 h (Table **2**, entries 1-6). Other copper salts led to the formation of **13a** in 18-42 % yield with the recovery of a bulk of substrate **13** (Table 2, entries 7-12). It is interesting to note the cuprous salt CuOAc, produced the **13a** in 72 % yield in 24 h (table 2, entry 13) and other metal acetate produced the same in 18-53 % yield (Table **2**, entry 14-16) which simply proved the importance of acetate ion. Additionally, the nitrating agents like $NaNO_3$ and $La(NO_3)_3$ produced the **13a** in 72 and 66 % yield respectively (table 2, entry **17-20**). Although use of $Fe(NO_3)_3$ and $Ca(NO_3)_2$ yield the product relatively in lesser quantity (table 2, entry 17 and 20). The high stoichiometric ratio of $Cu(OAc)_2$ (100 mol %) does not have any effect on the yield (Table **2**, entry 21). If no catalyst was added then there was no reaction (Table **2**, entry 22).

Table 2: Conditions screened[a].

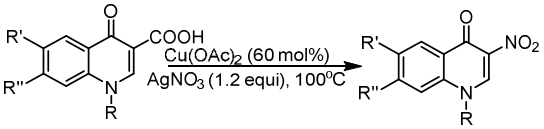


Entry	Lewis Acid	Amount (mol%)	MNO3[d]	Yield[b] (%)
1	$Cu(OAc)_2$	10	$AgNO_3$	12
2	$Cu(OAc)_2$	20	$AgNO_3$	35
3	$Cu(OAc)_2$	30	$AgNO_3$	55
4	$Cu(OAc)_2$	40	$AgNO_3$	65
5	$Cu(OAc)_2$	50	$AgNO_3$	87
6	$Cu(OAc)_2$	60	$AgNO_3$	92
7	$CuBr_2$	60	$AgNO_3$	18
8	CuF_2	60	$AgNO_3$	22
9	$CuMoO_4$	60	$AgNO_3$	34
10	$Cu(BF_4)_2$	60	$AgNO_3$	39
11	$CuSO_4$	60	$AgNO_3$	42
12	$Cu(OTf)_2$	60	$AgNO_3$	26
13	CuOAc	60	$AgNO_3$	72[c]
14	$Zn(OAc)_2$	60	$AgNO_3$	22
15	$Pd(OAc)_2$	60	$AgNO_3$	18
16	$Mn(OAc)_2$	60	$AgNO_3$	53
17	$Cu(OAc)_2$	60	$Fe(NO_3)_3$	62
18	$Cu(OAc)_2$	60	$NaNO_3$	72
19	$Cu(OAc)_2$	60	$La(NO_3)_3$	66
20	$Cu(OAc)_2$	60	$Ca(NO_3)_2$	59
21	$Cu(OAc)_2$	100	$AgNO_3$	90
22	----------		AgNO3	--[d]

[a] reaction condition: 3-carboxy-4-quinolones (**13**) (1 mmol), Cu Catalyst (60 mol%), AgNO3 (1.2 mmol), in water (1 M, with respect to quinolone), at 100°C. [b] Isolated Yield. [c] Reaction performed at 120°C.[d] Most of the nitrates used in hydrated forms.

The reaction was also screened in different solvents. We used a variety of polar and non-polar solvents (Table 3). Under different solvent condition, protic solvents were found to facilitate the formation of **13** in good yield (Table **3**, entry **5**). The unique property of water [26] encouraged us to use this as a solvent and fortunately we got excellent yield (Table **3**, entry 8).

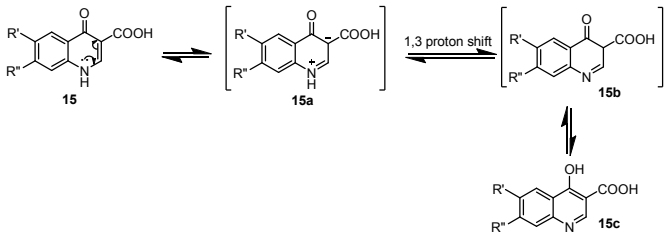
Table 3: Effect of solvent on the synthesis of 3-nitro-4-quinolones.[a]



Entry	Solvent	Yield %
1	DMF	56
2	DMSO	62
3	THF[b]	52
4	CH_3CN[b]	58
5	Ethanol[b]	72
6	DCM[b]	69
7	1,2-Dichloroethane[b]	66
8	H_2O	92

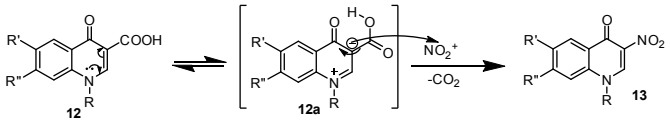
[a]Reaction condition: $Cu(OAc)_2$ 60 mol %, 1.2 equivalent $AgNO_3$ at 100°C. [b]reflux condition.

These satisfactory results led to explore the scope and limitation of this new environmental benign method. Therefore, various biologically important di halo quinolones containing different alkyl (methyl to octyl) groups at N1, were selected for nitration under the optimized reaction conditions to give corresponding 3-nitro derivatives. The results are listed (Table **5**). All the reactions were completed within 12-20 h in good to excellent yields. To further explored the utility of the reaction we tried to nitrate the 3-position of the quinolone without putting any substitution on N1- but after refluxing for about 24 h starting material was recovered without the traces of required compound. The recovery of starting material could easily be explained on the basis of 1, 3 shift of proton (Scheme **2**) coupled with –I effect of the carboxy group leading lesser availability of electron density at position 3, so less favourable reaction.



Scheme 2.Possibility of 1, 3 Shift which hindered the electrophilic attack over the position 3.

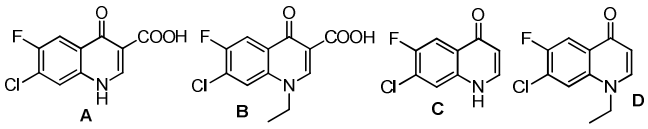
Nevertheless in case of N1 substituted substrate, there is no chance of 1, 3 proton shift so availability of electron density at position 3 leads to the formation of desired nitro derivatives (Scheme **3**).



Scheme 3. Mechanistic pathway to show the lack of 1, 3 Shift which facilitate the electrophilic attack over the position 3.

In order to explain the observed results we performed some computational studies where the energy minimized structures using MM2 protocol were subjected to electron density charge calculations in terms of Mullikan charges (Table **4**) on C3, C5 and C8 of the molecules shown in figure 3 by DFT using B3LYP basic set. This led to the observation that there is plenty of electron density over C3 position with respect of C5 and C8, for facilitating the nitration on this position (Figure **3**).

Table 4. Mullikan charges calculated over the different potions of the following molecules.



Entry	C3 (eV)	C5 (eV)	C8 (eV)
A	-0.214	-0.190	-0.143
B	-0.252	-0.187	-0.146
C	-0.270	-0.191	-0.145
D	-0.272	-0.190	-0.154

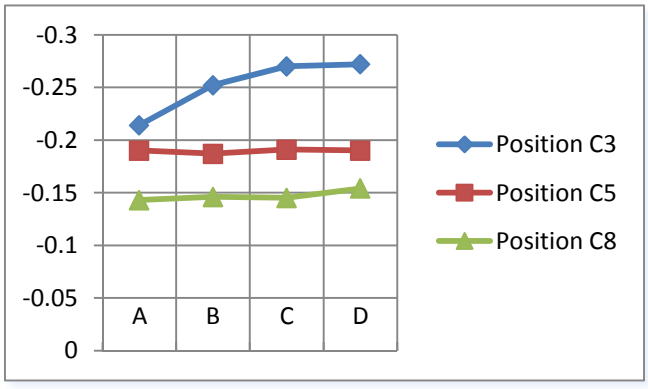
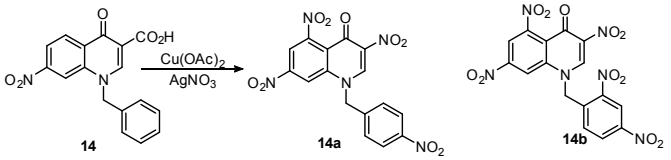


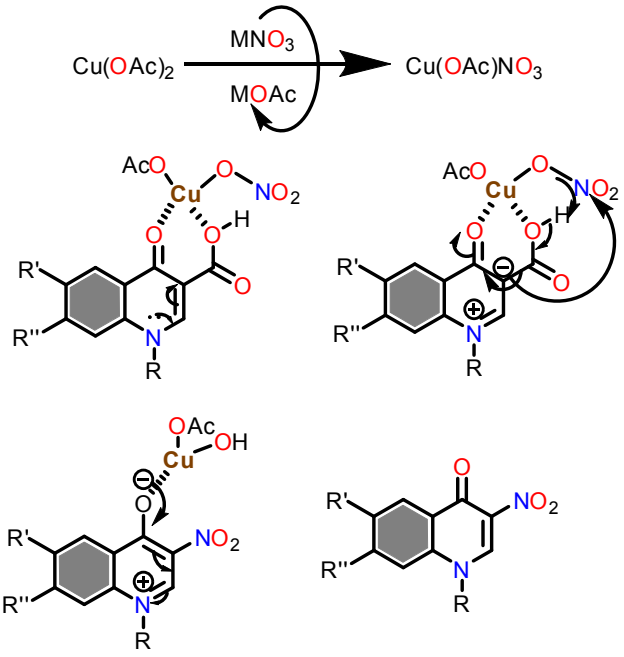
Figure 3. Graph chart of the Mulliken charges (electron Volts) calculated.

In order to widen the scope of this reaction the nitration of N1 benzylated quinolone **14** was carried out to see the effect of nitration on the aromatic ring of the alkyl aryl (benzyl) and aryl (4-nitro phenyl) group. This reaction led to multi spots on TLC. A detailed analysis based on NMR, IR and Mass spectrometry of the reaction products suggested the occurrence of over nitration especially on the phenyl ring as well as on the benzenoide part of the quinolone **14a** and **14b** (Scheme **4**)**.**



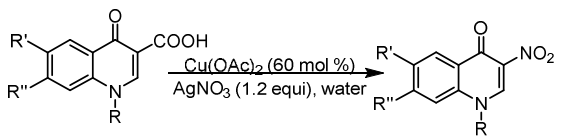
Scheme 4.Synthesis of 3-nitro N-aryl quinolone.

A plausible reaction mechanism was proposed for the copper-mediated chelation of β-keto acid assisted decarboxylative nitration of quinolone (Scheme 5).The two carbonyl group chelates with nitrate ion-containing copper(II) formed by an anion exchange between $Cu(OAc)_2$ and a nitrate salt, then decarboxylative nitration takes place through a concerted mechanism, in which NO_2 is attacked by the charge developed on the C-3 carbon and ionisable proton of acid took by the Cu-O to form Cu(OH)OAc.



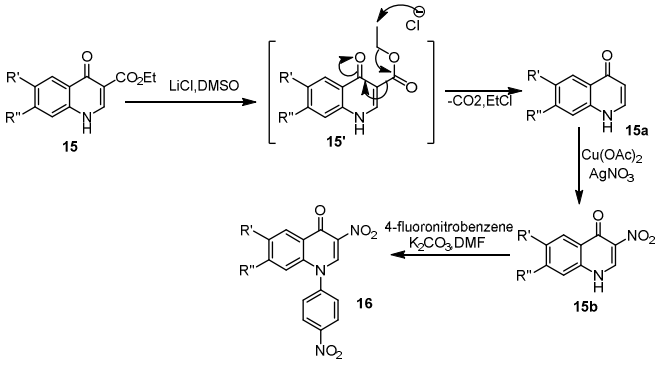
Scheme 5. Plausible Reaction Mechanism.

Table 5. Various di halo-3-carboxy-4-quinolone were investigated to be reacted with nitrating mixture to yield 3-nitro-4-qionolone.



S. No.	R	R', R"	Yield (%)	Time (h.)
13a.	Et	F/Cl	87	18
13b.	Isoprop	F/Cl	96	15
13c.	*n*-butyl	F/Cl	87	18
13d.	*sec*-butyl	F/Cl	84	16
13e.	hexyl	F/Cl	80	12
13f.	Me	F/F	82	12
13g.	n-propyl	F/F	81	16
13h.	*sec*-butyl	F/F	82	15
13i.	*n*-pentyl	F/F	89	16
13j.	*n*-octyl	F/F	87	18
13k.	Et	Cl/Cl	84	14
13l.	cyclo-prop	Cl/Cl	83	16
13m.	*n*-butyl	Cl/Cl	91	16
13n.	*sec*-butyl	Cl/Cl	82	18
13o.	heptyl	Cl/Cl	86	20

In order to overcome this problem and for getting the required N-alkyl aryl and aryl substituted 3-nitro-quinolone, the N1- substituted 3-ester was first decarboxylated by Krapcho decarboxylation (LiCl in DMSO) to give corresponding quinolone (**15a**) which on direct nitration followed by alkylation or arylation of the 3-nitoquinolne thus obtained gave the required N-arylated quinolones (Scheme 6).[27] The **15** when treated with Barton condition gives decarboxylated product which under optimized condition gives nitro quinolones in excellent yield.[28]



Scheme 6. General preparation of N-aryl 3-nitro quinolone via Krapcho decarboxylation.

Biological Evaluation

Some marketed antifilarial drugs like Nitazoxanide **17** and Tizoxanide **18** are known for their activities by the involvement of nitro group in their mode of action. A very recent example of antifilarial activity of 5-morpholin-4-yl-8-nitro-isoquinoline **19** reveals the importance of nitro group in the antifilarial activity.[29] Recently Srivastava et al. reported the quinolones as potential antifilarial agent.[30] In view of above we decided to evaluate the synthesised compound as antifilarial agents.

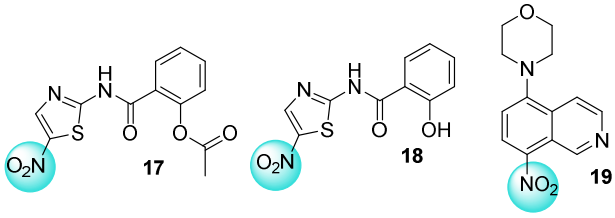


Figure 4. Some nitro group containing antifilarial agents.

All the synthesized quinolone based molecules (**13a-b, 14a** and **14b**) were evaluated for their *Brugia malayi* thymidylate kinase (BmTMK) inhibitory activity using a spectrophotometric assay. Some of these hybrid compounds showed significant inhibition of BmTMK. Among the fifteen tested hybrids, compound **14a** and **14b** were found to be the most potent compound of the series with IC_{50} value of 3.11 and 2.9 μM .

Docking Studies

In order to validate the selectivity of these compounds for filarial BmTMK as compared to human thymidylate kinase (hTK) the comparative docking was carried out. In this experiment all the synthesisewd compounds showed good binding affinity or selectivity towards BmTMK as compared to hTK enzyme. These compounds were also compared with the standard substrate TMP for validating the docking scores using template docking protocol from Molegro Virtual Docker 4.0. The docking study clearly supported the observations that these compounds selectively inhibit the filarial protein. The compound **14b** also showed one hydrogen bond interaction with the Arg-98. The compound also showed hydrogen bond interactions with Gly-103, His-70 and Thr-107 which may contribute its higher binding scores than the remaining molecules. It is also showing "pi-pi" stacking interactions with the Tyr-106, Phe-73, Phe-43 along with the hydrophobic interactions with these amino acids. In case of the **14a** it showed important interactions with amino acids viz. Arg-98, Lys-20 and Ser-21 along with the additional hydrophobic interactions with Ser-21, Tyr-106, Phe-73. The phenyl ring on the quinolone part of the molecule also forms "pi-pi" stacking interactions with the amino acids Phe-73 and Tyr-107 these interactions may contribute for the higher binding scores and affinities for filarial enzyme.

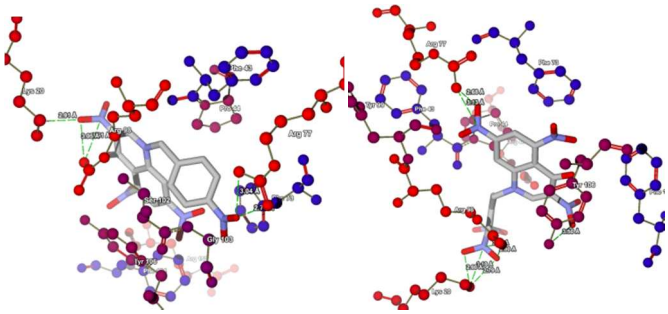


Figure 5. Molecular interactions of the compound **14a** and **14b** in the BmTMK active site.

Conclusions

In conclusion, a mild, environmental benign and cost effective one-pot procedure for the synthesis of 1-Alkyl-7-chloro-6-fluoro-3-nitro-4-quinolones via decarboxylation nitration method has been developed. The synthesised compounds were tested on the *Burgia malai* thymidaylate kinase enzyme. Out of all synthesized compounds **14a** and **14b** were most promising with IC_{50} values **3.11** and **2.9** respectively. These observed activities were further validated by molecular docking studies.

Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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