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Design, synthesis and biological evaluation of some novel 3-substituted acrylamide quinoline derivatives

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Abstract : A new series of 2,8-dichloroquinolin-3-acrylamide derivatives were designed by incorporating simple chemical methods. Here different N-substituted cyanoacetamide derivatives were used as the pharmacophore entities to link with the parent quinoline moiety and their microbial activity was screened, which has revealed that the few of the compounds were more potent than the corresponding standard drugs.
Key words: DIBAL-H, quinoline, cyanoacetamides, microbial activity.

Introduction:

Quinoline which is fused form of benzene and pyridine has significant history. These classes of heterocyclic compounds containing quinoline moieties have been used extensively for the treatment of malaria over many decades. 4-aminoquinolines have been very successful in the treatment of malaria because of their high efficacy, low toxicity & efficiency. In recent times chloroquine (CQ) has been used resistance against *P.falciparum*, it is also very effective against *P.ovale*, *P.vivax* as well a s *P.malariae*. Chloroquine is active against the blood stages of the parasite.

Quinine was the first quinoline compound that used as an anti-malarial. It consists of an (8S, 9R) quinuclidine-methanol group[1]. Pamaquine, an 8-aminoquinolin was discovered in 1920's is active against erythrocytic stages of malaria [2]. Primaquine, which is an analogue of pamaquine, is effective treatment against *P.vivax* liver infections [3,4]. Chloroquine was derived from quinacrine, a 4-aminoacridine, by conversion of its core to a chloroquinoline resulted in this very important anti-malarial drug.

Generally, for a drug a single-point mutation is sufficient to introduce resistance, in somecases multiple mutations are required. Chloroquine is able to accumulate to a greater extent inside of the digestive vacuole of sensitive parasite strains compared to resistant ones[5-7].

These mutations cause chloroquine to be expelled from the inside of the digestive vacuole[8].The importance of the quinoline nucleus has been well demonstrated and a number of biological activities have been associated with quinoline-containing compounds such as antiparasitic[9], anticancer[10], antiproliferative[11], anti-malarial[12], anti-inflammatory, anti-allergic[13] , & antibacterial[14] activities.

Over the past two decades, 2-chloroquinoline-3-carbaldehydes and their derivatives have excelled as considerable biological and pharmacological entities as anti-microbial[15,16] , anti-inflammatory[17,18], anti-malarial [19], and anti-virus activity[20].

P.Pitchai et al [21] prepared few novel indolyl-quinoline derivatives by photo-induced chemical reaction. β – anilinocrotonate under microwave irradiation afforded 2-methyl-4-hydroxy quinoline which was treated with iodine in presence of potassium iodide and sodium hydroxide to produce 2-methyl-4-hydroxy-3-iodo quinoline, where in the hydoxy group was treated with Phosphorous oxychloride and aniline to get the aniline derivative. This compound was taken in mixture of solvent of benzene and methanol along with iodine and sulfuric acid exposed to 400 watt mercury lamp for 48 hrs to get the indolyl-quinoline alkaloid.

Based on the importance of biological and chemical properties of quinoline derivatives **Sohrab Ghanei et al** [22] synthesized 2-chloro-3-hydrazino quinoline derivatives from 2-chloro-3-formyl quinolines in presence of TEA and acetic acid**.** All these compounds were screened for docking studies against non-nucleoside human HIV-1 reverse transcriptase (PDB Id: 1RT1). Binding energy and docking scores of the synthesized ligands revealed a promising resistance to the proliferation.

Ambika Srivatsava et al[23] prepared some biologically important chemical precursors from 3-formyl quinolines which were synthesized by using Vilmeier –Haack conditions from aromatic amines and N-arylacetamides and subsequently prepared few novel chemical entities which are presumed to be good biologically active compounds.

HM Meshram et al [24] prepared some novel 2,8-trifluoromethyl quinoline derivatives which were substituted with different chemical functionalities at position 3. By implementing the Suzuki coupling conditions, here an 3-Iodo derivative of 2,8-trifluoromethyl quinoline was treated with different aromatic, heterocyclic compounds. All these compounds were evaluated for cytotoxicity. Sensitivity of the compounds were tested with cell lines related to human Myeloid Leukemia (**HL-60**) and Leukemic monocyte lymphoma (**U937)** keeping Etoposide as standard drug.

AS Tekale et al [25] has achieved a facile synthesis of 3-formyl -2-chloro quinoline derivatives from o-methyl acetanilide with Vilsmeier reaction conditions. With the formyl derivatives a large number of Schiff's reagents were synthesized which were considered to be important chemical precursors for the many biologically active compounds.

Alka Mital et al [26] prepared biologically active bis (trifluoromethyl) quinoline derivatives which have anti tuberculosis activity. 2,8 trifluoromethyl-4-chloro quinoline was treated with various amines such as aliphatic , aromatic and heterocyclic and ended up with two novel series of compounds. All these compounds were screened for anti-TB activity by Microplate Alamar Blue Assay (MABA). The cytotoxicity was determined in VERO cell lines. Among ten compounds three compounds have exhibited great inhibitory activity.

A new series of thiozolidnediones of quinoline derivatives were prepared by **AL Srikanth** et al [27] which were tested for anti diabetic disease. Initially a 7-formyl-8-hydroxy quinoline was treated with an different aromatic substituted acetophenone in presence of strong base to afford an α,β-unsaturated compound, which was treated with thiozolidinedione derivative of fluoro benzyl compound under mild basic condition like sodium hydride . All the synthesized compounds were evaluated for anti diabetic study such as hypoglycemic activity by tail vein Method keeping Rosiglitazone as standard drug. Among the synthesized compounds only two compounds have shown considerable activity.

Ram Shankar Upadhayaya et al [28] carried out an extensive biological study on Mycobacterium tuberculosis (TB) such as synthesis, cytotoxicity and molecular docking. Some novel 2-methoxy-6-bromo quinoline derivatives with varied substitution at position 3 of quinoline moiety have been designed and synthesized. 2-methoxy-6-bromo-3-benzyl quinoline was initially treated with NBS to afford its bromo methylene derivative, after several steps ended up with different derivatives of malonic esters of 2-methoxy-6-bromo-3-benzyl quinoline. Cytotoxicity, docking study was carried out using Isoniazid as standard anti-TB drug. Out of several compounds only two compounds were competed with the standard drug.

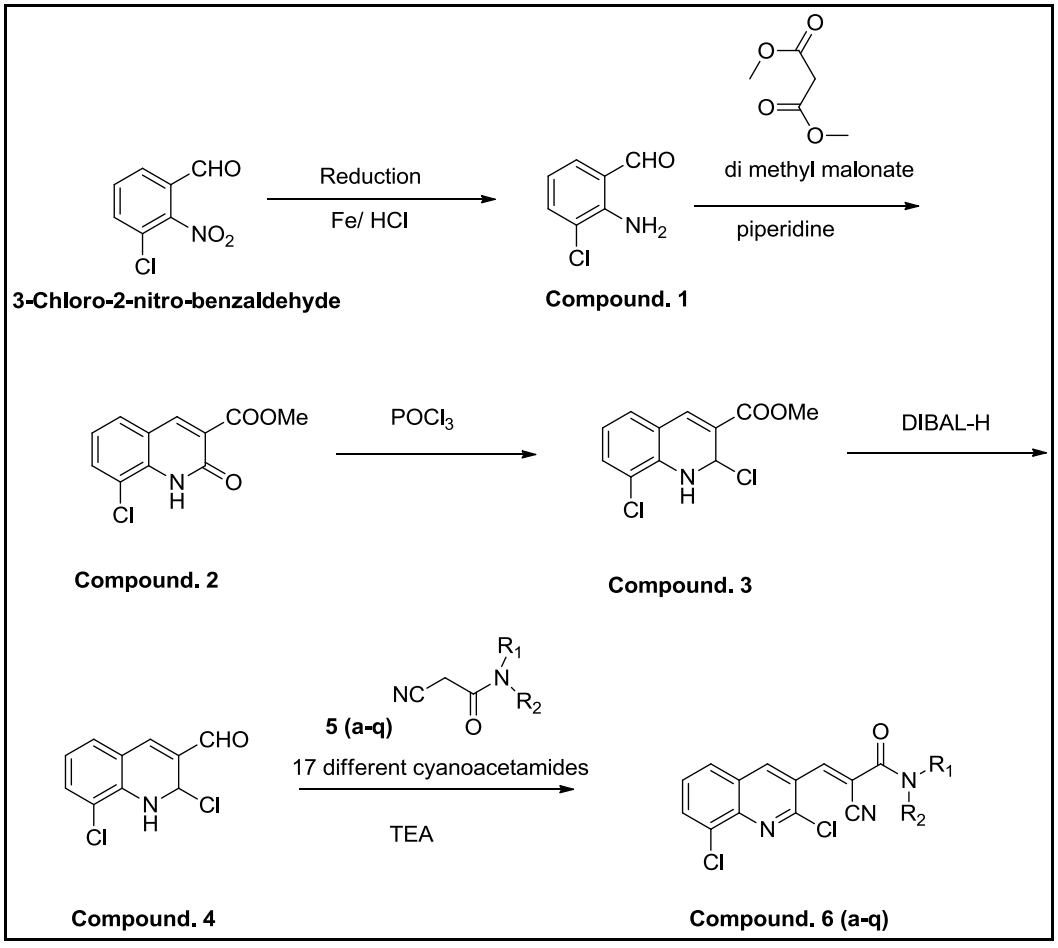
Mohamed Jawed Ahsan et al [29] prepared some new series of biologically active quinoline-2-one derivatives and screened for the anti cancer property. By treating 7-hydroxy-4-methyl coumarin with three different Carbazides afforded three different N-substituted quinoline-2-one derivatives. All these compounds were screened in-vitro anti cancer property such as human cervix cancer (HeLa) cell lines and human breast cancer (MDA-MB-435) cell lines. Also molecular docking study on epidermal growth factor receptor tyrosine kinase **(EGFR-TK)** was carried out. Only one compound has shown good docking score and strong hydrophobic interactions with eight amino acids of the target protein with dual hydrogen bonding.

As both quinolines and 1,2,3-triazoles have great and diverse biological applications, **Parthasaradhi Y et al** [30] has prepared new quinoline derivatives binding with 1,2,3 triazole at position 3. By reducing starting material 2-chloro-3-formyl-6-bromo quinoline with sodium borohydrate to afford the methanol derivative of quinoline compound. The alcohol was protected with methane sulfonyl chloride and treated with sodium azide to get the corresponding azide derivatives which was finally treated with aryl alkynes in presence of copper iodide and di isopropyl ethyl amine to afford the new series of compounds. All the compounds were screened for anti fungal, anti bacterial activity and anti malarial activity against P.falciparum.

In view of importance of pyrazole moiety, **Manjula Rani K et al**[31] have prepared a new series of quinolines fused with pyrazoles. 2-chloro-3-formyl quinoline derivatives were oxidized with potassium permanganate to get its acid derivatives, which were converted to ethyl esters followed hydrazine hydrate condensation afforded quinolino pyrazole derivatives which were considered as key input molecules for drug chemistry.

Experimental;

Procedures:



All amines and other key starting materials like 2-nitro-3-chloro benzaldehyde was purchased from Sigma Aldrich, malano nitrile was purchased from SD Fine chem, India. Thin layer chromatography was

performed on silicagel coated plates from from Macherey-Nagel-Germany, which were visualized by UV light and ninhydrin spray. Melting points were checked on Polman digital Melting point apparatus and are uncorrected. FT-IR spectra were recorded on Bucker Alpha-T.^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on a Varian 400 MHz spectrometer using DMSO-d^{6} and $CDCl_3$ as solvent. Mass spectra were recorded on an Agilent triple quadrapole mass spectrometer equipped with a turbo ion spray interface at 360 ^{o}C. Elemental analyses were performed using EA 1112 Thermo Finnigan instrument. The chemical methods adopted for the work has been represented in scheme-1.

2-nitro-3-chloro benzaldehyde (10 g, 0.0538 mol) was dissolved in ethanol (100 mL). Slowly the mass was heated to 65-70 °C, 1.0 mL hydrochloric acid was added. Iron powder (20 g, 0.3581 mol) was added in lot wise in 1.0 hr by keeping the mass in acidic side with the help of hydrochloric acid. After iron powder consumption was finished, the maintenance was extended to 1.0 hr at 65-70°C. Reaction was cooled to 50 °C and filtered through hyflo bed. The clear pale yellow solution was subjected to vacuum distillation. After complete distillation a pale brown color solid (**1**) (6.5 g, 78 %) was formed which was used directly in the next step.

Compound (1) (6.0 g , 0.0385 mol) was dissolved in ethanol and dimethyl malonate (5.6 g, 0.0423 mol) was added to this along with a two drops of piperidine, maintained the mass at reflux temperature for 2.0 hrs. Cooled the mass to 0-5 °C, after maintaining the mass at 0-5 °C, an off- white solid (**2**) (7.7 g, 85 % yield) was formed which was filtered[32].

To compound (**2)** (7.0 g, 0.0294 mol) was dissolved in Phosphorous oxy chloride (20 g) and maintained for 2.0 hrs at 70-75 °C. The reaction was monitored by TLC, after the completion of the reaction, the mass was cooled to RT and poured into crushed ice (100 g). The product was extracted with ethyl acetate (2 x 20 mL), the organic layer was dried with sodium sulfate, the clear solution after passing through hyflo bed was distilled off under vacuum. The crude mass **(3)** under nitrogen atmosphere was dissolved in toluene, cooled the mass to -15 °C to -10 °C, then slowly added DIBAL-H solution (20 mL) between -10 to -5 °C in 60 min, the reaction mass was maintained for 2.0 hrs, completion of reaction was monitored by TLC. After completion of the reaction, methanol (10 g in 15 mL water) was added drop-wise to the reaction mass at -10 to -5 °C, after the foam was ceased, water (25 mL) was added and separated the layers. The toluene layer was washed with 5 % dilute hydrochloric acid (25 mL) and 5% brine solution (25 mL). The organic layer was dried with sodium sulfate and distilled off completely. A pale brown color viscous mass (**4),** 5.0 g with 67 % yield was formed.[33, 34].

Compound (**4**) (50 mg, 0.0028 mol) was dissolved in ethanol (2.0 mL, catalytic amount of triethyl amine (TEA) and N-methyl-2-cyano acetamide (**5a**) (32 mg, 0.0033 mol)[35,36] was added. The reaction was maintained for 2.0 hrs at reflux, cooled the mass to RT, afforded an off white solid (**6a**), and was filtered through Buchner filter, which was dried at 50-55 ° C with a practical yield 75 %.

Similar reactions were performed with other N-substituted-2-cyano amide derivatives (**5a-q**) to afford different target compounds (**6a-q**). Yields were varied from 65-80% theoretically.

Biological activity [37]**:**

All the synthesized compounds were screened for anti-bacterial and anti fungal activity by using cup and plate method. Both activities were measured by zone inhibition on agar plates at 100 µg/mL. Anti bacterial activity was performed against two gram negative strains *Escherichia coli and Pseudomonas aeruginosa* and anti fungal activity was carried out against two fungal strains *Aspergillus niger* and *Candida albicans.* Flucanozole and streptomycin were used as standard anti fungal and anti bacterial drugs.

Compound	**Anti baterial**		**Anti fungal**	
code	E.coli	B.subtilis	A. niger	C. Albicans
5a	10	8	7	8
5b	10	7	14	10
5c	10	9	11	12
5d	11	14	8	10
5e	10	11	12	10
5f	12	9	14	14
5g	11	10	12	14
5h	15	14	10	12
5i	12	10	9	8
5j	**20**	**20**	**17**	**19**
5k	**21**	**20**	**22**	**22**
5l	15	14	12	14
5m	**21**	**23**	**18**	**17**
5n	**22**	**21**	**20**	**21**
5o	15	17	11	14
5p	10	15	15	12
5q	13	12	14	13
Streptomycin	20	19	0	0
Flucanozole	0	0	20	22

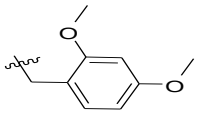
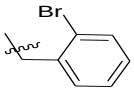
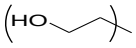
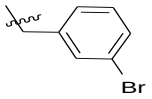
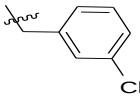
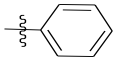
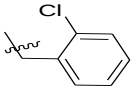
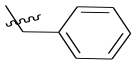
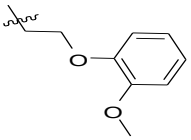
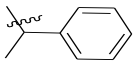
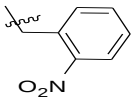
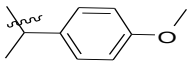
Results and discussions:

Compound (1) was prepared by reduction of 3-chloro nitro benzene with fine grade Iron powder in aqueous hydrochloric acid solution, the product was confirmed by comparing with authentic sample. Under Knoevenagel conditions, compound (1) was treated with dimethyl malonate along with one drop of piperidine, afforded 8-chloro quinolinone derivative which was chlorinated with phosphorous oxy chloride ($POCl_3$) followed by partial reduction with di iso propyl aluminium hydride (DIBAL-H) solution under nitrogen atmosphere to get 2,8-dichloro 3-formyl quinoline (compound 4). The formyl group formation was assigned by proton NMR at δ 10.6 and a sharp stretching band at 1766 cm^{-1}. The final step was again under knoevenagel reaction conditions treated with different N,N – substituted cyano acetamide derivatives. Here nearly 17 acetamides were used in the final condensation. All the compounds were isolated as crystalline solids. The final compounds structures were confirmed by spectral methods, Nitrile group was assigned by a sharp stretching absorption band at 2230 cm^{-1} in IR

On the other hand the formation of N-substituted acetamides were comes out as simple solids and semisolids with a yield range 60-76 % by simple chemical reaction between an amine and a 2-cyano acetamide in ethanol medium. Most of the compounds were compared by its previously reported authentic samples. These compounds were directly used in the final step.

The final step was a Knoevenagel condensation where in an aldehyde, compound (4) and an active methylene group (compounds, 5a-q) was refluxed under catalytic amount of organic base Triethylamine in ethanol. It is intended to prepare an unsaturated knoevenagel adduct, but the unsaturated adduct was in-situ cyclized with the adjacent –OH group to form an imino pyran, there by producing a novel tricyclic molecule. This was supported by both IR and Proton NMR, a characteristic –CN group was absent in IR due to its participation in formation of imino pyran ring. Similarly the absence of –OH proton reassures its participation in pyran ring formation.

Different amines used in cyanoacetamides for target compounds (6a-q).

Compound	R_1	R_2	Compound	R_1	R_2
5a	$-CH_3$	-H	5k		-H
5b	$-C_2H_5$	-H	5l		-H
5c		-H	5m		-H
5d		-H	5n		-H
5e		-H	5o		-H
5f		-H	5p		-H
5g		-H	5q		-H
5h		-H			
5i					
5j					

Spectral data:

1. (E)-2-cyano-3-(2, 8-dichloroquinolin-3-yl)-N-methyl acrylamide (6a)

IR (KBr, cm^{-1}): 3633 (-NH), 2212 (-CN), 1766 (-C=O), 1226 (-C-N), 1088 (-C-O).

^{1}H NMR ($CDCl_3$): δ 8.27 (s, H, C-4), 8.16 (s, H,-olefin), 7.93 (s, H,-NH), 7.90 (d, H, C-7), 7.68 (m, H, C-6), 7.43 (t, H, C-6), 2.73 (s, 3H,-Me).

^{13}C NMR ($CDCl_3$): δ 160 (-CO), 163 (olefinic), 160 (C-2), 141 (C-10), 136 (C-4), 133 (C-3), 131 (C-7, C-8), 129 (C-9), 127 (C-6, C-6), 116 (CN), 110 (C-CN), 26 (C, $-CH_3$)

MS: M^+ at m/z: 307.30

Anal.Calcd for $C_{14}H_9Cl_2N_3O$: C, 64.93; H, 2.96; Cl, 23.16; N, 13.73; O, 6.23, Found; C, 66.00; H, 3.00; Cl, 23.22; N, 13.60; O, 6.12.

2. (E)-2-cyano-3-(2,8-dichloroquinolin-3-yl)-N-ethyl acrylamide (6b)

IR (KBr, cm^{-1}): 3620 (-NH), 2221(-CN), 1760 (-C=O), 1220 (-C-N), 1100(-C-O).

^{1}H NMR ($CDCl_3$): δ 8.41 (s, H,-NH), 8.26 (s, H,C-4), 8.10 (s, H,-olefin), 7.86 (d, H, C-7), 7.66 (d, H, C-6), 7.40 (t, H, C-6), 3.20 (q, 2H,-CH_2), 1.13 (t,3H,-Me).

^{13}C NMR ($CDCl_3$): δ 169 (-CO), 166 (olefinic), 162 (C-2), 142 (C-10), 136 (C-4), 131 (C-3), 129 (C-7, C-8), 127 (C-9), 126 (C-6, C-6), 116 (CN), 108 (C-CN), 36 (C-CH_2), 20 (C,-CH_3).

MS: M^+ at m/z: 321.46

Anal.Calcd for $C_{16}H_{11}Cl_2N_3O$; C, 66.27; H, 3.46; Cl, 22.14; N, 13.12; O, 6.00, Found; C, 66.32; H, 3.40; Cl, 22.20; N, 13.20; O, 4.89

3. (E)-2-cyano-3-(2, 8-dichloroquinolin-3-yl)-N-(2-hydroxyethyl) acrylamide (6c)

IR (KBr, cm^{-1}): 3631(-NH), 2220 (-CN), 1746 (-C=O), 1289 (-C-N), 1102 (-C-O).

^{1}H NMR ($CDCl_3$): δ 8.60 (s, H,-NH), 8.20 (s, H,C-4), 8.00 (s, H,-olefin), 7.88 (d, H, C-7), 7.60 (d, H, C-6),7.41 (m, H, C-6), 4.86 (s, H, -OH), 3.69 (m, 2H, -OCH_2), 3.47 (m, 2H, -N-CH_2).

^{13}C NMR ($CDCl_3$): δ 162 (-CO), 168 (olefinic), 166 (C-2), 146 (C-10), 138 (C-4), 132 (C-3), 130 (C-7,C-8), 128 (C-9), 127 (C-6,C-6), 120 (CN), 112 (C-CN), 66 (O-CH_2), 41 (N-CH_2).

MS: M^+ at m/z: 339.16

Anal.Calcd for $C_{16}H_{11}Cl_2N_3O_2$: C, 63.69; H, 3.30; Cl, 21.09; N, 12.60; O, 9.62, Found; C, 63.61; H, 3.26; Cl, 21.20; N, 12.41; O, 9.42.

4. (E)-2-cyano-N-cyclopropyl-3-(2, 8-dichloroquinolin-3-yl) acrylamide (6d)

IR (KBr, cm^{-1}): 3490 (-NH), 2209 (-CN), 1746 (-C=O), 1230 (-C-N), 1100(-C-O).

^{1}H NMR ($CDCl_3$): δ 8.36 (s, H,-NH), 8.22 (s, H, C-4), 8.16 (s, H,-olefin), 7.90 (d, H, C-7), 7.66 (d, H, C-6), 7.40 (m, H, C-6), 3.26 (m, H, -CH, cyclopropyl), 0.6-0.8 (m, 4H, - 2xCH_2, cyclopropyl)

^{13}C NMR ($CDCl_3$): δ 160 (-CO), 166 (olefinic), 162 (C-2), 141 (C-10), 136 C-4), 134 (C-3), 131 (C-7,C-8), 128 (C-9), 126 (C-6, C-6), 118 (CN), 113 (C-CN), 28(C, cyclopropyl), 10 (2C, cyclopropyl).

MS: M^+ at m/z: 333.16

Anal.Calcd for $C_{16}H_{11}Cl_2N_3O$: C, 67.86; H, 3.34; Cl, 21.34; N, 12.66; O, 4.82, Found; C, 67.96; H, 3.40; Cl, 21.44; N, 12.66; O, 4.90

5. (E)-2-cyano-3-(2,8-dichloroquinolin-3-yl)-N-phenylacrylamide (6e)

IR (KBr, cm^{-1}): 3610 (-NH), 2220 (-CN), 1766 (-C=O), 1220 (-C-N), 1200(-C-O).

^{1}H NMR ($CDCl_3$) : δ 10.27 (s,-NH), 8.69 (s, H, olefin),8.16 (s, H, C- 4), 7 .90 (s, H, olefin), 7.66 (m, 2H, C'-2,C'-6), 7.43 (t, H, C-6), 7.26 (m, 2H, C'-3.C'-6), 7.07 (m, H, C'-4).

^{13}C NMR ($CDCl_3$): δ 166 (CO),166 (C, olefin), 162 (C-2), 146 (C-10), 138 (C'-1),136 (C-4), 133 (C-3), 131 (2C, C'-3, C'-6), 127 (C-9), 128 (C'-4), 128.9 (2C, C' -3, C'-6), 127.2 (C-6 ,C-6), 121.6 (C'-2,C'-6), 112.9 (C, CN), 116.8 (CN).

MS: M^+ at m/z: 369.40

Anal.Calcd for $C_{19}H_{11}Cl_2N_3O$: C, 61.98; H, 3.01; Cl, 19.26; N, 11.41; O, 4.34, Found; C, 62.00; H, 3.11; Cl, 19.32; N, 11.46; O, 4.29

6. (E)-N-benzyl-2-cyano-3-(2,8-dichloroquinolin-3-yl)acrylamide (6f)

IR (KBr, cm^{-1}): 3621(-NH), 2210(-CN), 1739 (-C=O), 1220 (-C-N), 1098 (-C-O).

^{1}H NMR ($CDCl_3$) : δ 10.27 (s, -NH), 8.69 (s, H, olefin), 8.16 (s, H, C- 4), 7 .90 (s, H, olefin), 7.66 (m, 2H ,C'-2,C'-6), 7.43 (t ,H, C-6), 7.26 (m, 2H, C'-3.C'-6), 7.07 (m, H, C'-4).

^{13}C NMR ($CDCl_3$): δ 166 (CO),166 (C, olefin), 162 (C-2), 146 (C-10), 138 (C'-1), 136 (C-4),133 (C-3), 131 (2C, C'-3, C'-6), 127 (C-9), 128 (C'-4), 128.9 (2C, C' -3, C'-6), 127.2 (C-6, C-6), 121.6 (C'-2, C'-6), 112.9 (C, CN), 116.8 (CN).

MS: M^+ at m/z: 383.30

Anal.Calcd for $C_{20}H_{13}Cl_2N_3O$: C, 62.84; H, 3.43; Cl, 18.66; N, 10.99; O, 4.19; Found; C, 62.90; H, 3.61; Cl, 18.60; N, 11.02; O, 4.16

7. 2-cyano-3-(2,8-dichloroquinolin-3-yl)-N-(1-phenylethyl)propanamide (6g)

IR (KBr, cm^{-1}): 3619(-NH), 2221(-CN), 1761 (-C=O), 1219 (-C-N), 1098(-C-O).

^{1}H NMR ($CDCl_3$) : δ 8.40 (s,-NH), 8.16 (s, H, olefin), 8.27 (s, H, C- 4), 7.90 (s, H, C-7), 7.86 (d, H, C-6), 7.43 (t ,H, C-6), 7.36 (m, 2H,C'-2, C'-6), 7.29 (m, 2H, C'-3.C'-6), 7.27 (t, H, C'-4), 4.97 (m, H, -N-CH), 1.48 (d, 3H, -Me).

^{13}C NMR ($CDCl_3$): δ 166 (C'-1), 169 (CO), 162(C, olefin), 160 (C-2), 142 (C-10), 136 (C-4), 132 (C-3), 130.2 (C-6,C-6),128 (2C, C'-3, C'-6), 126 (C-9), 126 (C'-2, C'-6), 124 (C'-4), 116.8 (CN), 109 (C, C- CN), 62.7 (C, N-CH), 21.6 (C, Me).

MS: M^+ at m/z: 397.10

Anal.Calcd for $C_{21}H_{16}Cl_2N_3O$: C, 63.66; H, 3.82; Cl, 17.89; N, 10.60; O, 4.04 ,Found; C, 63.78; H, 3.90; Cl, 17.86; N, 10.66; O, 4.00.

8. (E)-2-cyano-3-(2,8-dichloroquinolin-3-yl)-N-(1-(4-methoxyphenyl)ethyl)acrylamide (6h)

IR (KBr, cm^{-1}): 3620(-NH), 2210 (-CN), 1748 (-C=O), 1219 (-C-N), 1110 (-C-O).

^{1}H NMR ($CDCl_3$) : δ 8.46 (s, -NH), 8.30 (s, H, C- 4), 8.20 (s, H,olefin), 7.92 (s, H, C-7), 7.88 (d, H, C-6), 7.48 (t, H, C-6), 7.26 (m, 2H, C'-2, C'-6), 6.86 (m, 2H, C'-3.C' -6), 6.10 (m, H, -N-CH), 4.00 (s, 3H, -OMe), 1.61 (d,3H,-Me).

^{13}C NMR ($CDCl_3$): δ 160 (C'-4), 168 (CO), 166 (C, olefin), 162 (C-2),140 (C-10), 136 (C'-1), 134 (C-4), 131 (C-3), 129 (2C, C-6, C-6), 127 (C-9),126 (C'-2, C'-6), 120 (2C, C' -3, C'-6), 118 (CN), 110 (C, C- CN), 66 (C, -OMe), 42 (C, -N-CH), 26 (C, Me).

MS: M^+ at m/z: 427.16

Anal.Calcd for $C_{22}H_{17}Cl_2N_3O_2$: C, 61.99; H, 4.02; Cl, 16.63; N, 9.86; O, 7.61, Found; C, 62.01; H, 4.08; Cl, 16.66; N, 9.96; O, 7.46.

9. (E)-3-(2,8-dichloroquinolin-3-yl)-2-(pyrrolidine-1-carbonyl)acrylonitrile (6i)

IR (KBr, cm^{-1}): 3487 (-NH), 2228 (-CN), 1764 (-C=O), 1240 (-C-N), 1180 (-C-O).

^{1}H NMR ($CDCl_3$): δ 8.27 (s, H, C-4), 8.11 (s, H, olefin), 7.90 (d, H, C-7), 7.86 (d, H, C-6), 7.43 (t, H, C-6), 3.28 (t, 4H, -N $(CH_2)_2$), 1.80 (t, 4H, 2xCH_2, piperidine).

^{13}C NMR ($CDCl_3$): δ 170 (CO), 163.6 (CH=C), 160 (C-2), 141 (C-10), 136 (C-4), 132 (2C, C-7, C-8), 128 (C-9), 126 (2C, C-6, C-6), 116 (CN), 113 (C-CN), 49 (2C, pyrrolidine), 26 (2C, pyrrolidine).

MS: M^+ at m/z: 347.26

Anal.Calcd for $C_{17}H_{13}Cl_2N_3O$: C, 68.98; H, 3.78; Cl, 20.48; N, 12.14; O, 4.62.

Found; C, 69.02; H, 3.86; Cl, 20.61; N, 12.10; O, 4.66.

10. (E)-3-(2,8-dichloroquinolin-3-yl)-2-(morpholine-4-carbonyl)acrylonitrile (6j)

IR (KBr, cm^{-1}): 3499 (-NH), 2298 (-CN), 1499 (-C=O), 1209 (-C-N), 1099 (-C-O).

^{1}H NMR ($CDCl_3$): δ 8.32 (s, H, C-4), 8.06 (s, H, olefin), 7.90 (d, H, C-6), 7.86 (d, H, C-6), 7.40 (t, H, C-6), 3.66 (s, 8H, morpholine).

^{13}C NMR ($CDCl_3$): δ 168 (CO), 166 (CH=C), 149 (C-2), 138 (C-10), 136 (C-4), 132 (C-3), 130 (2C, C-7, C-8), 127 (C-9), 124 (2C, C-6, C-6), 118 (CN), 112 (C-CN), 66 (2C, morpholine), 48 (2C, morpholine).

MS: M^+ at m/z: 366.10

Anal.Calcd for $C_{17}H_{13}Cl_2N_3O_2$: C, 66.37; H, 3.62; Cl, 19.67; N, 11.60; O, 8.83, Found; C, 66.26; H, 3.66; Cl, 19.46; N, 11.70; O, 8.90

11. (E)-2-cyano-3-(2,8-dichloroquinolin-3-yl)-N-(2,4-dimethoxybenzyl)acrylamide (6k)

IR (KBr, cm^{-1}): 3620 (-NH), 2220 (-CN), 1762 (-C=O), 1210 (-C-N), 1120 (-C-O).

^{1}H NMR ($CDCl_3$) : δ 8.96 (s, -NH), 8.27 (s, H, C- 4), 8.20 (s, H, olefin), 8.10 (s, H, C-7), 7.86 (d, H, C-6), 7.42 (t, H, C-6), 7.26 (m, H, C'-6), 6.66 (d, 2H, C' -3.C' -6), 3.89 (s, 3H, -OMe), 1.26 (d, 2H, -N-CH_2).

^{13}C NMR ($CDCl_3$): δ 169 (C' -4), 167 (CO), 166 (C' -2), 163 (C, olefin), 148 (C-2), 142 (C-10), 136 (C'-1), 137 (C-3), 134 (C-4), 131 (2C, C-7, C-8), 129 (C' -6), 127 (2C, C-6, C-6),126 (C-9), 123 (C' -1), 120 (CN) 118 (C, C-CN), 106.6 (C'-6), 102 (C' -3), 60 (2C, 2x-OMe), 36 (C, -N-CH_2).

MS: M^+ at m/z: 443.36

Anal.Calcd for $C_{22}H_{17}Cl_2N_3O_3$: C, 69.74; H, 3.87; Cl, 16.03; N, 9.60; O, 10.86, Found C, 60.02; H, 3.91; Cl, 16.00; N, 9.46; O, 10.76

12. (E)-N-(2-bromobenzyl)-2-cyano-3-(2,8-dichloroquinolin-3-yl)acrylamide (6l)

IR (KBr, cm^{-1}): 3612 (-NH), 2229 (-CN), 1739 (-C=O), 1289 (-C-N), 1130(-C-O).

^{1}H NMR ($CDCl_3$) : δ 8.66 (s, -NH), 8.31 (s, H, C- 4), 8.22 (s, H, olefin), 8.00 (s, H, C-7), 7.80 (d, H, C-6), 7.66 (m, 2H, C-6, C'-3), 7.27 (m, H, C'-6), 6.17 (d, H, C'-6), 7.06 (t, H, C'-4), 4.62 (s, 2H, -N-CH_2).

^{13}C NMR ($CDCl_3$): δ 169 (C'-4), 167 (CO), 166 (C'-2), 163 (C, olefin), 148 (C-2), 142 (C-10), 136 (C'-1), 137 (C-3), 134 (C-4), 131 (2C, C-7, C-8), 129 (C'-6), 127 (2C, C-6, C-6), 126 (C-9), 123 (C'-1), 120 (CN) 118 (C, C-CN), 106.6 (C'-6), 102 (C'-3), 60 (2C, 2x-OMe), 36 (C,-N-CH_2).

MS: M^+ at m/z: 462.10

Anal.Calcd for $C_{20}H_{12}BrCl_2N_3O$: C, 62.09; H, 2.62; Br, 17.33; Cl, 16.37; N, 9.11; O, 3.47, Found ; C, 62.12; H, 2.66; Br, 17.41; Cl, 16.41; N, 9.06; O, 3.46

13. (E)-N-(3-bromobenzyl)-2-cyano-3-(2,8-dichloroquinolin-3-yl)acrylamide (6m)

IR (KBr, cm^{-1}): 3600(-NH), 2222 (-CN), 1766 (-C=O), 1226 (-C-N), 1110(-C-O).

^{1}H NMR ($CDCl_3$) : δ 8.92 (s, -NH), 8.29 (s, H, C- 4), 8.16 (s, H, olefin), 8.00 (s, H, C-7), 7.76 (d, H, C-6), 7.66 (t, H, C'-4), 7.44 (s, H, C'-2), 7.31 (t, H, C-6), 7.27 (t, H, C'-6), 7.00 (d, H, C'-6), 4.38 (s, 2H, -N-CH_2).

^{13}C NMR ($CDCl_3$): δ 162 (CO), 166 (C'-2), 166 (C, olefin), 160 (C-2), 146 (C'-1), 142 (C-10), 136 (C-3), 134 (C-4), 132 (2C, C-7, C-8), 130 (C'-1), 128.6 (C'-6), 127 (C-9), 126 (2C, C-6, C-6), 123 (C'-6), 120 (C'-3), 118 (CN), 116 (C-2), 111 (C-CN), 46 (C, -N-CH_2).

MS: M^+ at m/z: 460.00

Anal.Calcd for $C_{20}H_{12}BrCl_2N_3O$: C, 62.09; H, 2.62; Br, 17.33; Cl, 16.37; N, 9.11; O, 3.47. Found; C, 62.11; H, 2.80; Br, 17.60; Cl, 16.26; N, 9.16; O, 3.60

14. (E)-N-(3-chlorobenzyl)-2-cyano-3-(2,8-dichloroquinolin-3-yl)acrylamide (6n)

IR (KBr, cm^{-1}): 3489 (-NH), 2210 (-CN), 1739 (-C=O), 1200 (-C-N), 1120(-C-O).

^{1}H NMR ($CDCl_3$) : δ 8.88 (s, -NH), 8.30 (s, H, C- 4), 8.19 (s, H, olefin), 8.06 (s, H, C-7), 7.81 (d, H, C-6), 7.66 (m, 2H, C-6, C'-2), 7.36 (m, 2H, C'-4, C'-6), 7.20 (d, H, C'-6), 4.66 (s, 2H, -N-CH_2).

^{13}C NMR ($CDCl_3$): δ 166 (CO), 160 (C, olefin), 166 (C'-2), 148 (C'-1), 144 (C-10), 138 (C-4), 136 (C'-3), 133 (C-3), 130 (2C, C-7, C-8), 128 (2C, C'-2, C'-6), 126 (C-9), 124 (2C, C-6, C-6), 122 (C'-4), 120 (C'-6), 117 (CN), 111 (C, C-CN), 44 (C, -N-CH_2).

MS: M^+ at m/z: 417.61

Anal.Calcd for $C_{20}H_{12}Cl_3N_3O$: C, 67.66; H, 2.90; Cl, 26.62; N, 10.08; O, 3.84, Found; C, 67.71; H, 2.86; Cl, 26.60; N, 10.16; O, 3.76

15. (E)-N-(2-chlorobenzyl)-2-cyano-3-(2,8-dichloroquinolin-3-yl)acrylamide (6o)

IR (KBr, cm^{-1}): 3600 (-NH), 2220 (-CN), 1760 (-C=O), 1209 (-C-N), 1098 (-C-O).

^{1}H NMR ($CDCl_3$) : δ 8.96 (s, -NH), 8.36 (s, H, olefin), 8.26 (s, H, C-4), 8.00 (s, H, C-7), 7.83 (d, H, C-6), 7.68 (d, H, C'-3), 7.46 (t, H, C-6) 7.30 (t, H, C'-4), 7.21 (m, 2H, C'-6, C'-6), 4.33 (s, 2H, -N-CH_2).

^{13}C NMR ($CDCl_3$): δ 161 (CO), 167 (C, olefin), 160 (C-2), 146 (C'-1), 141 (C-10), 136 (C-4), 133 (C-3), 131 (C'-2), 129 (2C, C-7, C-8), 126 (C, C'-3), 124 (C'-6), 124 (C'-4), 122 (C-9), 120 (2C, C-6, C-6), 116 (CN), 110 (C, C-CN), 38 (C, -N-CH_2).

MS: M^+ at m/z: 417.61

Anal.Calcd for $C_{20}H_{12}Cl_3N_3O$: C, 67.66; H, 2.90; Cl, 26.62; N, 10.08; O, 3.84, Found; C, 67.80; H, 2.81; Cl, 26.46; N, 10.11; O, 3.66

16. (E)-2-cyano-3-(2,8-dichloroquinolin-3-yl)-N-(2-(2-methoxyphenoxy)ethyl)acrylamide (6p)

IR (KBr, cm^{-1}): 3600 (-NH), 2216 (-CN), 1766 (-C=O), 1210 (-C-N), 1110 (-C-O).

^{1}H NMR ($CDCl_3$) : δ 8.66 (s, -NH), 8.41 (s, H, olefin), 8.23 (s, H, C-4), 7.96 (s, H, C-7), 7.80 (d, H, C-6), 7.43 (t, H, C-6), 6.94 (m, 2H, C'-3, C'-6), 6.88 (m, 2H, C'-4, C'-6), 4.20 (t, 2H,-OCH_2), 3.80 (s, 3H, -OMe), 3.10 (t, 2H, -NCH_2).

^{13}C NMR ($CDCl_3$): δ 163 (CO), 163 (C, olefin), 161 (C-2), 160 (C'-1), 143 (C-10), 137 (C-4), 132 (C-3), 131 (2C, C-7, C-8), 128 (C-9), 126 (2C, C-6, C-6), 123 (C'-6), 120 (2C, C'-4, C'-6), 116 (C-2), 112 (C'-3) ,116 (CN),109 (C, C-CN), 70 (C, -OCH_2), 66 (C, OMe), 40 (C, -N-CH_2).

MS: M^+ at m/z: 443.61

Anal.Calcd for $C_{22}H_{17}Cl_2N_3O_3$;C, 69.74; H, 3.87; Cl, 16.03; N, 9.60; O, 10.86, Found; C, 69.86; H, 3.90; Cl, 16.00; N, 9.46; O, 10.80

17. (E)-2-cyano-3-(2,8-dichloroquinolin-3-yl)-N-(2-nitrophenyl)acrylamide (6q)

IR (KBr, cm^{-1}): 3620(-NH), 2222(-CN), 1760 (-C=O), 1223 (-C-N), 1110 (-C-O).

^{1}H NMR ($CDCl_3$) : δ 10.08 (s, -NH), 8.60 (s, H, C'-6), 8.33 (d, H, C'-3), 8.26 (s, H, C- 4), 8.16 (s, H, olefin),7.90 (d, H, C'-6), 7.80 (d, H, C-7), 7.60 (d, H, C-6), 7.40 (t, H, C'-4), 7.26 (t, H, C-6).

^{13}C NMR ($CDCl_3$): δ 161 (CO), 164 (C, olefin), 161 (C-2), 146.6 (C' -2), 136 (C-4), 133 (C-3), 131 (C-7, C-8), 128 (2C, C'-1, C'-9), 126 (C-6), 124.9 (2C, C'-4, C'-3), 116.8 (CN), 112.9 (C, C-CN).

MS: M^+ at m/z: 414.26

Anal.Calcd for $C_{19}H_{10}Cl_2N_4O_3$; C, 66.23; H, 2.44; Cl, 17.16; N, 13.66; O, 11.62. Found; C, 66.20; H, 2.46; Cl, 17.10; N, 13.60; O, 11.66

Conclusions:

By adopting simple chemical methods a new series of 2,8-dichloro quinoline derivatives with various acrylamides substituted at 3rd position were synthesized. All the compounds were screened anti bacterial and anti fungal activity. Most of the compounds have exhibited prominent microbial activity than the corresponding standard reference drugs. These compounds would serve as new series of quinoline compounds in medicinal chemistry.

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References:

1. E. Leete, *Acc. Chem.Res*., 1969, 2, 69.
2. M. Schlitzer, *Chem MedChem*, 2007, 2, 944.
3. N. Vale, R. Moreira and P. Gomes, *Eur. J. Med. Chem*., 2009, 44, 937.,
4. W. R. J. Taylor and N. *J. White, Drug safety*, 2004, 27, 26.
5. R. E. Martin, R. V. Marchetti, A. L. Cowan, S. M. Howitt, S. Broer and K. Kirk, *Science*, 2009, 326, 1680.
6. M. Foley and L. Tilley, *Int. J. Parasitol*. , 1997, 27, 231.
7. D. J. Krogstad, I. Y. Gluzman, D. E. Kyle, S. K.Martin, W. K. Milhous and P. H. Schlesinger, *Science, 1987*, 238, 1283.
8. D. A. Fidock, T. Nomura, A. K. Talley, R. A. Cooper, S. M. Dzekunov, M. T. Ferdig, L. M.B. Ursos, A. bir Singh Sidhu, B. Naudé, K. W. Deitsch, X. Su, J. C. Wootton, P. D. Roepe, T. E. Wellems, *Mol. Cell*., 2000, 6, 861.
9. Abadi, A. H.; Brun, R. *Arzneimforsch Drug Res*. 2003, 63, 666.
10. Dlugosz, A.; Dus, D. *Farmaco* 1996, 61, 367.
11. Croisy-Delcey, M.; Coroisy, A.; Carrez, D.; Huel, C.; Chiaroni, A.; Ducrot, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem*. 2000, 8, 2629
12. Jain, R.; Jain, S.; Gupta, R. C.; Anand, N.; Dutta, G. P.; Puri, S. K. *Indian J. Chem*. 1994, 33B, 261.
13. Cairns, H.; Cox, D.; Gould, K. J.; Ingall, A. H.; Suschitzky, J. L. *J. Med. Chem*. 1986, 28, 1832.
14. Mohammed, A.; Abdel-Hamid, N.; Maher, F.; Farghaly, A. *Czech. Chem. Commun.* 1992, 6, 1647.
15. S. Paul and R. Gupta, ; *Indian Journal of Chemical Technology*, vol. 6, 263–266, 1998.
16. R. Gupta, S. Paul, P. Kamotra, and A. K. Gupta*: Indian Journal of Heterocyclic Chemistry*, vol. 7, no. 2, pp. 166–166, 1997.
17. F. Herencia, M. L. Ferr´andiz, A. Ubeda et al; *Bioorganic and Medicinal Chemistry Letters, v*ol. 8, no. 10, pp. 1169–1174,1998.
18. O. A. El-Sayed, M. El-Semary, and M. A. Khalil, *Alexandria Journal of Pharmaceutical Sciences, v*ol. 10, no. 1, pp. 43–46, 1996.
19. M. Sekar and K. J. R. Prasad, ; *Journal of Chemical Technology and Biotechnology* , 72, 60–64, 1998.
20. M. R. Bell and J. H. U. S. Ackerman, *US, 4920128 ,1990*.
21. P.Pitchai, PS Mohan, RM Gengan, . *Ind.jrnl Chem*.48B, 2009, 692-696.
22. Sohrab Ghanei, Hossein Eshghi, Jalil Lari, Mohammad Saadatmandzadeh; *Journal of Chemical and Pharmaceutical Research*, 2016, 7(2):428-433.

23. Ambika Srivatsava and RM Singh, *Ind. Journal of Chemistry*.44B, 2006, 1868-1876
24. HM Meshram, B.Chennakeshava reddy, D.Aravind Kumar, M Kalyan, P Ramesh, P Kavitha and J Venkateswara Rao. *Ind.Jrnl.Chem*.61B, 2012,1411-1416.
25. AS Tekale, SS Mudhekar, SAL Sahaik: Vilsmeier-Haack reagent. *Int.Jrnl of Chemical studies.*2016, 2(6),42-46.
26. Alka Mital, Villendra Singh Negi, Uma Ramachandran; *Arkivok*,2006, 1424- 6376, 220-227.
27. L Srikanth, N Raghunandan, P Srinivas, G Amarender Reddy; *Int.jrnl of pharma and bio sciences*,.2010; vol.1,issue 4,122-131
28. Ram Shankar Upadhayaya, Jaya Kishore Vandavasi, Nageswara Rao Vasireddy, Vivek Sharma, Shailesh S. Dixit, Jyoti Chattopadhyaya; *Bioorganic & Medicinal Chemistry*, 17 (2009) 2830–2841;
29. Mohamed Jawed ahsan, Rita yadav, Surender singh Jadav, *1st international electronic conference on medicinal chemistry*.2016,2-27
30. Parthasaradhi Y, Suresh S, Ranjith Kumar B,Savitha Jyostna T., *Orbital electronic journal of chemistry*.2016,1984-6428,7,3,264-269
31. Manjula Rani K , Rajendran SP ; *Int jrnl of innovative Res. In Science, Engineering and technology;* 2014,3,9,16966-16973.
32. A. Mc Chuskey, P.J. Robinson, T. Hill, J.L. Scott, J.K. Edwards, Tetrahedron Lett. 43, 3117–3120 (2002)
33. K. Wang, K. Nguyen, Y. Huang, A. Domling. *J. Comb. Chem*. 11, 920–927 (2009)
34. A.P. Tamiz, S.X. Cai, Z.L. Zhou, P.W. Yuen, R.M. Schelkun, E.R. Whittemore, E. Weber, R.M.Woodward, J.F. Keana ; *J.Med. Chem*. 42, 3412–3420 (1999)
35. S. Chandrasekhar, M. Suresh Kumar, B. Muralidhar ; *Tetrahedron Letters*: 39, 8, 19, 1998, 909–910
36. H. D Dickson, S. C. Smith, K. W. Hinkle, *Tetrahedron Lett*., 2004, 46, 6697-6699
37. V. Bobbarala, P.K. Katikala, K.C. Naidu, S. Penumajji,. *Indian. J. Sci. Technol*. 2(4), 87– 90 (2009)

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