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Design, Synthesis, Characterization and Biological evaluation of (4-(7-chloroquinolin-4-yl)piperazin-1-yl)(substitutedphenyl)methanones as antimicrobial agents

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ABSTRACT

A series of (4-(7-chloroquinolin-4-yl)piperazin-1-yl)(substitutedphenyl)methanones were prepared via multistep synthesis which involved acrylation without base, cyclisation, hydrolysis, decarboxylation, electrophilic chlorination reactions and subsequent chloro-amine coupling with various substituted benzoyl chloride derivatives. The structure of the synthesized compounds was established by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. All the novel compounds have been tested on thin layer chromatographic plate for purity and evaluated for their antimicrobial activity against gram positive and gram negative bacteria which demonstrated moderate to good antimicrobial activity.

***Keywords*:** Chloroquinoline, piperazine, multistep synthesis, antimicrobial agents

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1. INTRODUCTION

In recent years, organic research on synthesis of novel nitrogen containing heterocyclic ring system is attracting much attention. Over the years of active research, quinoline pharmacophore in many marketed drugs and important structural unit widely existing in alkaloids, therapeutics and synthetic analogues with exciting biological activities[1]. Quinoline and its derivatives are well known for their antimalarial and therapeutic properties[2]. The quinoline nucleus occurs in several natural compounds (e.g. cinchona alkaloids) and pharmacologically active substances displaying a broad range of biological activity[3]. Quinoline derivatives constitute an important class of compounds for new drug development.

Pharmaceutically important quinoline containing molecules such as amidoquine[4] and chloroquine[5] are found as an anti-malarial marketed drug in which a chlorine atom is attached at the C-7 position according to quinoline ring, while the pharmaceutically important quinolone containing molecules such as norfloxacine[6], Ciprofloxacin[7] and levofloxacin[8] contain a fluorine atom which is attached at the C-6 position and piperazine ring at the C-7 position according to quinolone moiety (Fig. 1). In a recent times, a number of synthesis of chloroquinoline and fluoroquinolone analogues have been reported, together with the corresponding anti-malarial activity and structure activity relationship (SAR) studies[9,10]. As a result, much effort has been put forward for the synthesis of quinoline based heterocycles in recent times by synthetic chemist.

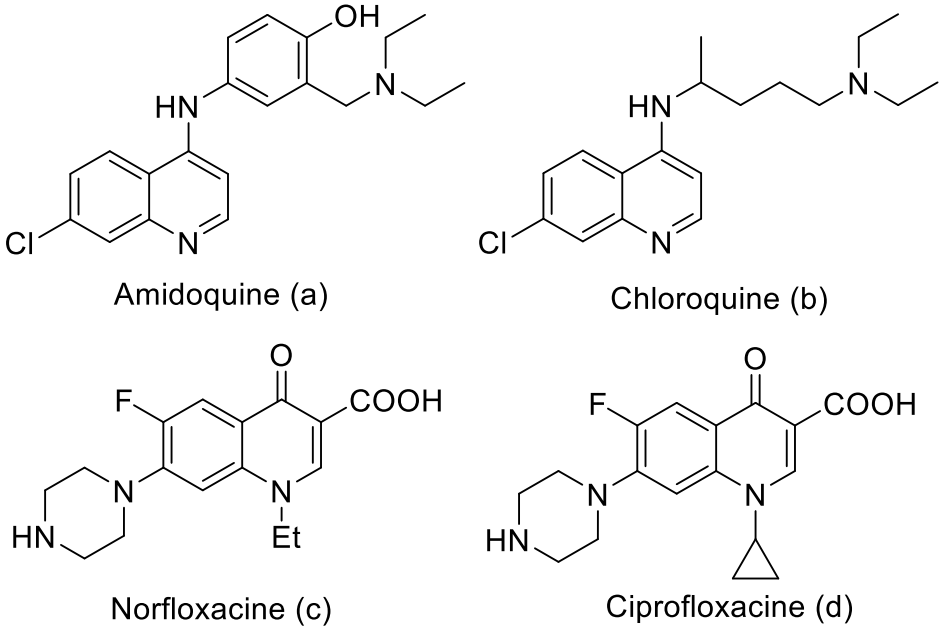


Figure 1. Biologically active quinoline containing analogs.

The major pharmaceutically importance observation have been guiding that a quinoline derivatives possess varied biological activities such as anticancer activity[11] antimycobacterial activity[12], antimicrobial activity[13-16], anticonvulsant activity[17,18], anti-inflammatory activity (NSAIDs)[19,20], cardiovascular activity[21,22]. A number of methods have been reported for the

synthesis of quinoline derivatives such as Lewis acid and catalytic synthesis[23]. We have demonstrated a very efficient and environmentally benign strategy for the synthesis of new benzoylic analogues of 7-chloro-4-(piperazin-1-yl)quinoline derivatives with good to excellent yields. Our research group is associated with synthesis and evaluation of biological activities of nitrogen containing heterocyclic ring system from last few decade[24-28]. As from the above demonstrated facts of medicinal importance of nitrogen containing heterocyclic ring system, we have planned to synthesize some new derivatives of (4-(7-chloroquinolin-4-yl)piperazin-1-yl)(substitutedphenyl)methanones and evaluate its antimicrobial activities in respect to standard drugs.

2. EXPERIMENTAL

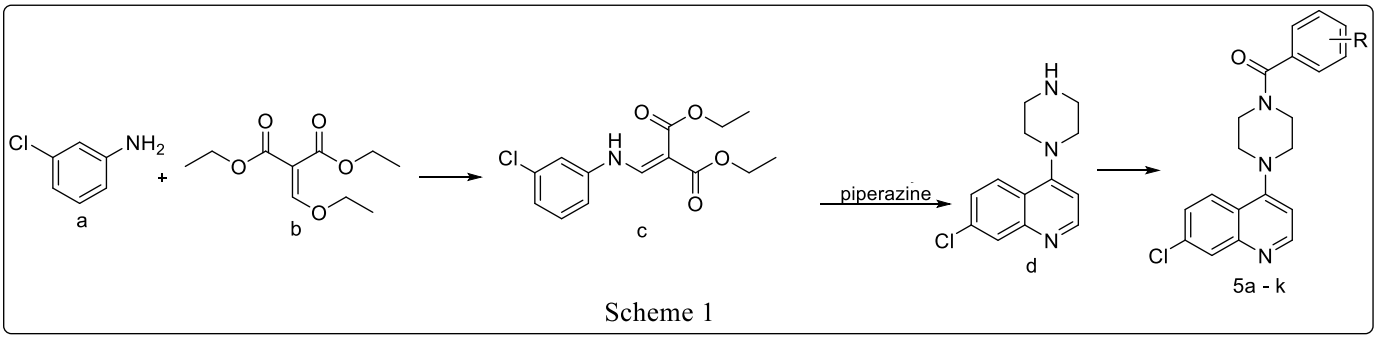
2. 1. Materials and methods

Indicated, all chemicals were purchased and used without any further purification. Reactions were monitored by thin layer chromatography (TLC) on DC 60 F_{254} silica Kieselgel-G plates of 0.5 mm thickness, TLC spots were visualized by UV-light irradiation. Melting point was determined using a Buchi B-540 capillary apparatus and are uncorrected. IR data were recorded on a Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method and are expressed in cm^{-1} (KBr).

NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR) and chemical shifts are referenced to the solvent residual signals with respect to tetramethylsilane; ^{1}H NMR chemical shifts are designated using the following abbreviations as well as their combinations: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, *br* = broad signal, coupling constant in Hz, ^{13}C NMR spectra are protondecoupled. Elemental analysis of all the synthesized compounds were carried out on Euro EA 3000 elemental analyser and the results are in agreements with the structures assigned.

2. 2. Chemistry

In the present study, the synthesis of title compound (5a-k) is outlined in **scheme 1**, it was achieved by multistep reactions involved acrylation, cyclisation, hydrolysis, decarboxylation, electrophilic chlorination and chloro-amine coupling reaction. All the reaction steps are performed by simple, efficient, rapid and scalable method with high yield and purity. As well, in this section to achieved that objective of work.



Scheme 1

2. 3. Mechanistic study

The plausible mechanism for these reaction steps is outlined in Fig. 2. Initial nucleophilic attack of the amino group of compound, 1, on the C=C of the malonate, 2, side chain followed by loss of one molecule of EtOH yielded, 3. The compound, 3, undergoes to cyclization reaction in presence of higher temperature followed enol formation by the loss of EtOH to yielded, 4, the hydrolysis of compound, 4, in the presence of base with water to yielded compound, 5, which on removal of CO_2 by the decarboxylation process under high temperature to yield, 6, further conversion of hydroxyl to chloro group in the presence of chlorinating agent to produce compound, 7, Subsequent, chloro-amine coupling between compound, 7, with piperazine to achieve the targeted scaffold (Fig. 2).

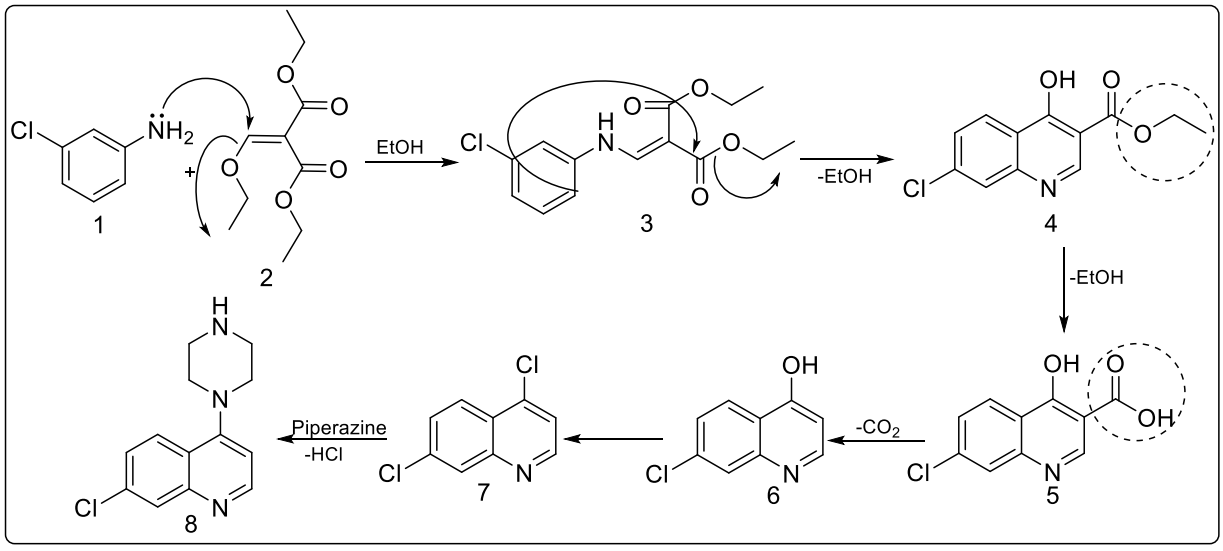


Figure 2. Plausible reaction mechanism

2. 4. Synthesis of diethyl 2-(((3-chlorophenyl)amino) methylene)malonate (c)

A solution of 3-chloroaniline (a) (39.19 mmol) in 50 mL of ethanol. To the above was added diethyl (ethoxymethylene)malonate (b) (39.19 mmol) directly. The suspension was stirred for 120 min at 80 °C. Upon completion of the reaction monitored by TLC, the mixture was concentrated under reduced pressure. The resulting precipitate was filtered off and washed with 2x10 mL of n-hexane. The crude material was obtain as a white solid and forwarded to next step without further purification. M.p. 65-67 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.005-10.971 (*d*, *J* = 13.6, 1H), 8.465-8.431 (*d*, *J* = 13.6, 1H), 7.307-7.261 (*qt*, *J* = 2.4, 10.4, 1H), 7.129-7.091 (*m*, 2H), 7.048-6.987 (*m*, 1H), 4.331-4.231 (*m*, 4H), 1.394-1.321 (*m*, 6H).

2. 5. Synthesis of 7-chloro-4-(piperazin-1-yl)quinoline (d)

To synthesis of targeted molecule, multistep reaction was carried out. First step involve cyclization reaction of 2-(((3-chlorophenyl)amino)methylene)malonate (c) (13.464 mmol) with diphenyl ether (134.64 mmol) at 240 ºC for 4.5 hrs after workup to obtain crude solid product. Then hydrolysis of this product (6.572 mmol) will be carried out by LiOH (26.29 mmol) in 30

mL of THF/Water (1:1) at 65 ºC for 10 hrs, afterwards acidic workup afford the desired product. Decarboxylation of this product (7.174 mmol) perform with diphenyl ether (71.74 mmol) at 240 ºC for 2 hrs then diluted with n-Hexane, after filtration of the reaction mixture and dried under vacuum to afford the desired product. Subsequent, electrophilic chlorination of the resulted product (7.262 mmol) carry out by using $POCl_3$ (65.35 mmol) at room temperature for 48 hrs, upon workup obtain crude product which are carry forwarded to next step. The reaction of resulted product (5.076 mmol) with an excess of piperazine (25.38 mmol), using N-methylpyrrolidinone (NMP) as the solvent, with Et_3N (6.091 mmol) as the base and a catalytic amount of K_2CO_3, after workup afforded the desired product as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.712-8.700 (*d, J* = 4.8, 1H), 8.032-8.027 (*d, J* = 2.0, 1H), 7.953-7.931 (*d, J* = 8.8, 1H), 7.422-7.393 (*d, J* = 11.2, 2H), 6.824-6.812 (*d, J* = 4.8, 1H), 3.252-3.157 (*t, J* = 38, 8H).

2. 6. General procedure for the synthesis of (4-(7-chloroquinolin-4-yl)piperazin-1-yl) (substitutedphenyl)methanone (5a-k)

Take 7-chloro-4-(piperazin-1-yl)quinoline (d) (2.018 mmol) and substituted benzoyl chloride (2.825 mmol) in 10 mL of chloroform as a solvent and triethyl amine (6.055 mmol) as a base in 50 mL RBF, the reaction mixture was stirred at room temperature for 1 hr. Upon completion of the reaction was monitored by TLC, reaction mixture is poured in water and extracted with ethyl acetate, dried over Na_2SO_4, evaporated under reduced pressure and titurated with n-Hexane to obtain analytical grade pure product. All products were characterised by FT-IR, ^{1}H NMR, ^{13}C NMR, Mass analysis and melting point by comparison with literature data (Table 1).

Table 1. Physical Constant table of (4-(7-chloroquinolin-4-yl)piperazin-1-yl) (substituted-phenyl)methanones (5a-k).

Comp. Code	Substituent R=	Molecular Formula	Molecular Weight	Yield (%)	M.P. (ºC)
5a	2-F	$C_{20}H_{17}ClFN_3O$	369.82	83	83-85
5b	4-NO_2	$C_{20}H_{17}ClN_4O_3$	396.83	87	81-83
5c	3-Cl	$C_{20}H_{17}Cl_2N_3O$	386.28	77	90-92
5d	4-Cl	$C_{20}H_{17}Cl_2N_3O$	386.28	79	87-89
5e	3-Br	$C_{20}H_{17}BrClN_3O$	430.73	73	86-88
5f	2,3-Cl_2	$C_{20}H_{16}Cl_3N_3O$	420.72	66	93-95
5g	2-OCH_3	$C_{21}H_{20}ClN_3O_2$	381.86	85	95-97
5h	4-CH_3	$C_{21}H_{20}ClN_3O$	365.86	92	90-92
5i	4-F	$C_{20}H_{17}ClFN_3O$	369.82	80	89-91

5j	4-OCH_3	$C_{21}H_{20}ClN_3O_2$	381.86	83	82-84
5k	3-OCH_3	$C_{21}H_{20}ClN_3O_2$	381.86	85	85-87

2. 7. Spectral data for representative compound

(4-(7-chloroquinolin-4-yl)piperazin-1-yl)(2-fluorophenyl)methanone (5a)

Yield: 0.62 g (83%); M.p. 83-85 ºC, IR (KBr, υ in cm^{-1}): 2848.96 (C-H stretching in aromatic), 1639.55 (C=O stretching in amide), 1579.75 (aromatic ring skeleton), 1448.59 (C=C stretching in aromatic ring), 1371.43 (C-N stretching in aromatic ring), 1286.56 (C-N med), 1145.75 (C-F stretching), 1006.88 (C=C bending), 945.15 (C-C Bending), 875.71 (C-H bending), 754.19 (C-Cl Stretching), 696.33 (o-disubstituted aromatic ring); Ms: *m/z* [M^+] 369.00; Anal. Cal. for $C_{20}H_{17}ClFN_3O$: C, 64.96; H, 4.63; N, 11.36; Found: C, 64.84; H, 4.52; N, 11.24.

(4-(7-chloroquinolin-4-yl)piperazin-1-yl)(4-nitrophenyl)methanone (5b)

Yield: 0.69 g (87%); M.p. 81-83 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.776-8.763 (*d*, *J*=5.2, 1H), 8.344-8.317 (*m*, 2H), 8.078-8.073 (*d*, *J*=2.0, 1H), 7.957-7.935 (*d*, *J*=8.8, 1H), 7.670-7.643 (*m*, 2H), 7.485-7.457 (*dd*, *J*=2.4, 9.2, 1H), 6.876-6.864 (*d*, *J*=4.8, 1H), 4.113 (*s*, 2H), 3.696 (*s*, 2H), 3.326 (*s*, 2H), 3.181 (*s*, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.25, 156.09, 151.97, 150.14, 148.57, 141.42, 135.32, 129.15, 128.21, 126.82, 124.55, 124.07, 121.75, 109.46, 52.06, 47.65, 42.24, 8.62; IR (KBr, υ in cm^{-1}): 2843.17 (C-H Stretching in aromatic), 1639.55 (C=O stretching in amide), 1575.89 (aromatic ring skeleton), 1518.03 (N-O stretching), 1440.87 (C=C stretching in aromatic ring), 1344.43 (C-N stretching in aromatic ring), 1276.92 (C-N med), 1008.80 (C=C bending), 927.79 (C-C bending), 862.21 (C-H bending), 817.85 (p-disubstituted aromatic ring), 769.62 (C-Cl stretching); Ms: *m/z* [M^+] 396.00; Anal. Cal. for $C_{20}H_{17}ClN_4O_3$: C, 60.53; H, 4.32; N, 14.12; Found: C, 60.42; H, 4.20; N, 14.07.

(3-chlorophenyl)(4-(7-chloroquinolin-4-yl)piperazin-1-yl)methanone (5c)

Yield: 0.60 g (77%); M.p. 90-92 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.763 (*s*, 1H), 8.075 (*s*, 1H), 7.962-7.940 (*d*, *J*=8.8, 1H), 7.474-7.338 (*m*, 5H), 6.873-6.862 (*d*, *J*=4.4, 1H), 4.072 (*s*, 2H), 3.735 (*s*, 2H), 3.292-3.180 (*d*, *J*=44.8, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.04, 156.28, 151.96, 150.12, 137.01, 135.26, 134.79, 130.23, 130.10, 129.09, 127.33, 126.73, 125.22, 124.67, 121.80, 109.42, 52.41; IR (KBr, υ in cm^{-1}): 2837.38 (C-H Stretching in aromatic), 1627.97 (C=O stretching in amide), 1579.75 (aromatic ring skeleton), 1448.59 (C=C stretching in aromatic ring), 1379.15 (C-N stretching in aromatic ring), 1278.85 (C-N med), 1012.66 (C=C bending), 933.58 (C-C bending), 868.00 (C-H bending), 765.77 (C-Cl stretching), 748.41 (m-disubstituted aromatic ring); Ms: *m/z* [M^+] 385.00; Anal. Cal. for $C_{20}H_{17}Cl_2N_3O$: C, 62.19; H, 4.44; N, 10.88; Found: C, 62.11; H, 4.31; N, 10.81.

(4-chlorophenyl)(4-(7-chloroquinolin-4-yl)piperazin-1-yl)methanone (5d)

Yield: 0.63 g (79%); M.p. 87-89 ºC, IR (KBr, υ in cm^{-1}): 2827.74 (C-H Stretching in aromatic), 1647.26 (C=O stretching in amide), 1564.32 (aromatic ring skeleton), 1419.66 (C=C stretching in aromatic ring), 1379.15 (C-N stretching in aromatic ring), 1273.06 (C-N med), 1008.80 (C=C

bending), 927.79 (C-C bending), 862.21 (C-H bending), 831.35 (p-disubstituted aromatic ring), 754.19 (C-Cl stretching); Ms: *m/z* [M^+] 385.00; Anal. Cal. for $C_{20}H_{17}Cl_2N_3O$: C, 62.19; H, 4.44; N, 10.88; Found: C, 62.12; H, 4.32; N, 10.81.

(3-bromophenyl)(4-(7-chloroquinolin-4-yl)piperazin-1-yl)methanone (5e)

Yield: 0.58 g (73%); M.p. 86-88 ºC, IR (KBr, υ in cm^{-1}): 2837.38 (C-H Stretching in aromatic), 1629.90 (C=O stretching in amide), 1577.82 (aromatic ring skeleton), 1448.59 (C=C stretching in aromatic ring), 1379.15 (C-N stretching in aromatic ring), 1278.85 (C-N med), 1012.66 (C=C bending), 931.65 (C-C bending), 866.07 (C-H bending), 798.56 (m-disubstituted aromatic ring), 756.12 (C-Cl stretching); Ms: *m/z* [M^+] 429.00; Anal. Cal. for $C_{20}H_{17}BrClN_3O$: C, 55.77; H, 3.98; N, 9.76; Found: C, 55.70; H, 3.89; N, 9.69.

(4-(7-chloroquinolin-4-yl)piperazin-1-yl)(2,3-dichlorophenyl)methanone (5f)

Yield: 0.55 g (66%); M.p. 93-95 ºC, IR (KBr, υ in cm^{-1}): 2823.88 (C-H Stretching in aromatic), 1629.90 (C=O stretching in amide), 1575.89 (aromatic ring skeleton), 1425.44 (C=C stretching in aromatic ring), 1383.01 (C-N stretching in aromatic ring), 1282.71 (C-N med), 1010.73 (C=C bending), 929.72 (C-C bending), 868.00 (C-H bending), 794.70 (m-disubstituted aromatic ring), 744.55 (C-Cl stretching) 713.69 (o-disubstituted aromatic ring); Ms: *m/z* [M^+] 419.00; Anal. Cal. for $C_{20}H_{16}Cl_3N_3O$: C, 57.10; H, 3.83; N, 9.99; Found: C, 56.99; H, 3.74; N, 9.92.

(4-(7-chloroquinolin-4-yl)piperazin-1-yl)(2-methoxyphenyl)methanone (5g)

Yield: 0.65 g (85%); M.p. 95-97 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.761-8.749 (*d*, *J*=4.8, 1H), 8.070-8.065 (*d*, *J*=2.0, 1H), 7.067-7.945 (*d*, *J*=8.8, 1H), 7.473-7.446 (*dd*, *J*=2.0, 8.8, 1H), 7.382-7.362 (*d*, *J*=8.0, 2H), 7.268-7.238 (*t*, *J*=12, 2H), 6.864-6.852 (*d*, *J*=4.8, 1H), 4.060 (*s*, 2H), 3.776 (*s*, 2H), 3.233-3.197 (*br*, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.84, 156.44, 151.96, 150.13, 140.32, 135.19, 132.32, 130.65, 129.59, 129.24, 129.06, 127.29, 126.64, 124.76, 121.83, 109.38, 52.38, 21.45; IR (KBr, υ in cm^{-1}): 2829.69 (C-H Stretching in aromatic), 1620.26 (C=O stretching in amide), 1575.89 (aromatic ring skeleton), 1419.66 (C=C stretching in aromatic ring), 1377.22 (C-N stretching in aromatic ring), 1292.35 (C-N med), 1008.80 (C=C bending), 927.79 (C-C bending), 866.07 (C-H bending), 752.26 (C-Cl stretching), 640.39 (o-disubstituted aromatic ring); Ms: *m/z* [M^+] 381.00; Anal. Cal. for $C_{21}H_{20}ClN_3O_2$: C, 66.05; H, 5.28; N, 11.00; Found: C, 65.96; H, 5.17; N, 10.91.

(4-(7-chloroquinolin-4-yl)piperazin-1-yl)(p-tolyl)methanone (5h)

Yield: 0.68 g (92%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.690-8.678 (*d*, *J*=4.8, 1H), 7.997-7.992 (*d*, *J*=2.0, 1H), 7.895-7.872 (*d*, *J*=9.2, 1H), 7.400-7.372 (*dd*, *J*=2.0, 9.2, 1H), 7.309-7.289 (*d*, *J*=8.0, 2H), 7.195-7.165 (*t*, *J*=12, 2H), 6.790-6.778 (*d*, *J*=4.8, 1H), 3.975 (*br*, 2H), 3.702-3.636 (*br*, 2H), 3.147 (*br*, 4H), 2.327 (*s*, 3H); IR (KBr, υ in cm^{-1}): 2989.76 (C-H stretching in alkane), 2831.60 (C-H Stretching in aromatic), 1633.76 (C=O stretching in amide), 1572.04 (aromatic ring skeleton), 1421.58 (C=C stretching in aromatic ring), 1379.15 (C-N stretching in aromatic ring), 1280.78 (C-N med), 1010.73 (C=C bending), 927.79 (C-C bending), 864.14 (C-H bending), 821.70 (p-disubstituted aromatic ring), 750.33 (C-Cl stretching); Ms: *m/z* [M^+] 365.00; Anal. Cal. for $C_{21}H_{20}ClN_3O$: C, 68.94; H, 5.51; N, 11.49; Found: C, 68.87; H, 5.45; N, 11.42.

(4-(7-chloroquinolin-4-yl)piperazin-1-yl)(4-fluorophenyl)methanone (5i)

Yield: 0.60 g (80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.776-8.764 (*d*, *J*=4.8, 1H), 8.083-8.078 (*d*, *J*=2.0, 1H), 7.972-7.949 (*d*, *J*=9.2, 1H), 7.517-7.456 (*m*, 3H), 7.172-7.129 (*t*, *J*=17.2, 2H), 6.875-6.862 (*d*, *J*=5.2, 1H), 4.047 (*br*, 2H), 3.784 (*br*, 2H), 3.242-3.108 (*br*, 4H); IR (KBr, υ in cm^{-1}): 2837.38 (C-H Stretching in aromatic), 1627.97 (C=O stretching in amide), 1575.89 (aromatic ring skeleton), 1462.09 (C=C stretching in aromatic ring), 1377.22 (C-N stretching in aromatic ring), 1276.92 (C-N med), 1157.33 (C-F stretching), 1012.66 (C=C bending), 927.79 (C-C bending), 864.14 (C-H bending), 821.70 (p-disubstituted aromatic ring), 758.05 (C-Cl stretching); Ms: *m/z* [M^+] 369.00; Anal. Cal. for $C_{20}H_{17}ClFN_3O$: C, 64.96; H, 4.63; N, 11.36; Found: C, 64.88; H, 4.57; N, 11.31.

(4-(7-chloroquinolin-4-yl)piperazin-1-yl)(4-methoxyphenyl)methanone (5j)

Yield: 0.64 g (83%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.782-8.772 (*d*, *J*=4.0, 1H), 8.088-8.084 (*d*, *J*=1.6, 1H), 7.992-7.970 (*d*, *J*=8.8, 1H), 7.493-7.463 (*t*, *J*=12.0, 3H), 6.980-6.958 (*d*, *J*=8.8, 2H), 6.884-6.871 (*d*, *J*=5.2, 1H), 3.944-3.871 (*m*, 7H), 3.248 (*br*, 4H); IR (KBr, υ in cm^{-1}): 2833.52 (C-H Stretching in aromatic), 1627.97 (C=O stretching in amide), 1570.11 (aromatic ring skeleton), 1417.73 (C=C stretching in aromatic ring), 1381.08 (C-N stretching in aromatic ring), 1251.84 (C-N med), 1014.59 (C=C bending), 927.79 (C-C bending), 866.07 (C-H bending), 815.92 (p-disubstituted aromatic ring), 765.77 (C-Cl stretching), 713.69 (methoxy stretching); Ms: *m/z* [M^+] 381.00; Anal. Cal. for $C_{21}H_{20}ClN_3O_2$: C, 66.05; H, 5.28; N, 11.00; Found: C, 65.98; H, 5.16; N, 10.92.

(4-(7-chloroquinolin-4-yl)piperazin-1-yl)(3-methoxyphenyl)methanone (5k)

Yield: 0.65 g (85%); IR (KBr, υ in cm^{-1}): 2833.52 (C-H Stretching in aromatic), 1631.83 (C=O stretching in amide), 1575.89 (aromatic ring skeleton), 1423.51 (C=C stretching in aromatic ring), 1379.15 (C-N stretching in aromatic ring), 1288.49 (C-N med), 1010.73 (C=C bending), 935.51 (C-C bending), 868.00 (C-H bending), 790.84 (m-disubstituted aromatic ring), 750.33 (C-Cl stretching), 711.76 (methoxy stretching); Ms: *m/z* [M^+] 381.00; Anal. Cal. for $C_{21}H_{20}ClN_3O_2$: C, 66.05; H, 5.28; N, 11.00; Found: C, 65.97; H, 5.17; N, 10.90.

3. ANTIMICROBIAL ACTIVITY

All the synthesized compounds were screened *in vitro* for their antimicrobial activity. For evaluation of antibacterial activity *staphylococcus aureus* MTCC 96 and *streptococcus pyogenes* MTCC 442 from gram positive group of bacterial strain and *escherichia colli* MTCC 443 and *pseudomonas aeruginosa* MTCC 1688 from gram negative group of bacterial strain have been used. For evaluation of antifungal activity *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323 have been used as a fungal strains.

Micro broth dilution method[29-31] has been utilised to determine minimal inhibition concentrations (MIC), and evaluate the antibacterial activity. It is one of the non-automated in vitro bacterial susceptibility tests. This classic method yields a quantitative result for the amount of antimicrobial agents that is needed to inhibit growth of specific microorganisms. The MIC values of compounds 5a-k and standard drug against selected microbes are presented in following Table 2.

Table 2. Antimicrobial screening of compounds 5a-k as a MIC.

Comp. Code	Antibacterial activity				Antifungal activity		
	Minimum inhibitory concentration µg/ml				Minimum inhibitory concentration µg/ml		
	Gram +*ve* Bacteria		Gram -*ve* Bacteria				
	S. Aureus	***S. pyogenus***	***E. coli***	***P. Aeruginosa***	***C. albicans***	***A. niger***	***A. Clavatus***
5a	250	**100**	125	200	**250**	250	250
5b	250	**100**	250	**100**	**500**	250	250
5c	**125**	250	250	250	1000	500	**125**
5d	250	**100**	125	500	1000	250	250
5e	**100**	**62.5**	200	**100**	**500**	1000	1000
5f	250	**100**	250	200	1000	**125**	250
5g	**100**	250	200	200	**250**	250	**125**
5h	250	250	250	250	1000	250	250
5i	**125**	**100**	**62.5**	250	**250**	250	500
5j	**100**	200	250	200	**500**	250	250
5k	250	**62.5**	250	250	**250**	1000	500
A.	250	100	100	100	-	-	-
Cl.	50	50	50	50	-	-	-
C.	50	50	25	25	-	-	-
N.	-	-	-	-	100	100	100
G.	-	-	-	-	500	100	100
A: Ampiciliin, **Cl**: Chloramphenicol, **C**: Ciprofloxacin, **N**: Nystatin, **G**: Greseofulvin							

Abbreviations: *S. aureus, Staphylococcus aureus*; *S. pyogenus, Streptococcus pyogenes; E. coli, Escherichia coli*; *P. aeruginosa, Pseudomonas aeruginosa*; *C. albicans, Candida albicans*; *A. niger, Aspergillus niger; A. clavatus, Aspergillus clavatus;*

Some synthesized compounds were more active towards the bacterial strains that we had considered for studies in comparison to the standard drugs.

For antibacterial activity, the compounds 5e, 5g and 5j (100 μg/ml) were found to be more active against *S. aureus* with respect to the standard drug ampicillin. Compounds 5e and 5k (62.5 μg/ml) showed excellent activity against *S. pyogenus* with respect to standard drugs ampicillin, ciprofloxacin and chloramphenicol. Compounds 5i (62.5 μg/ml) showed more activity against *E. coli* with respect to standard drug ciprofloxacin and chloramphenicol. Moderate activity against *P. aeruginosa* with respect to standard drug ciprofloxacin and chloramphenicol and comperative with respect to standard drug ampicillin was shown by compounds 5b and 5e (100 μg/ml).

For antifungal activity, compounds 5g, 5i and 5k (250 μg/ml) showed better activity against *C. albicans* with respect to standard drug greseofulvin while Compounds 5b, 5e and 5j (500 μg/ml) showed comparative activity against *C. albicans* with respect to standard drug greseofulvin. Compound 5f (125 μg/ml) showed moderate activity against *A. niger* with respect to standard drugs greseofulvin and nystatin while compound 5c and 5g (125 μg/ml) showed moderate activity against *A. clavatus* with respect to standard drugs greseofulvin and nystatin. From the results obtained, it could be interpreted that compounds with electron withdrawing group substitution showed moderate activity compared to those possessing electron donating group substitution.

4. RESULT AND DISCUSSION

The synthetic path of targeted molecule was described in Scheme 1, Mechanistic study in Figure 2 and Physical constant in Table. The targeted molecules 5a to 5k were synthesize by multistep synthetic approach involved acrylation, cyclisation, hydrolysis, decarboxylation, electrophilic chlorination and chloro-amine coupling reaction.

We have confirmed the structure by spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. Molecular ion peak was observed in agreement with molecular weight of respective compound. The IR spectrum of synthesized compounds exhibited characteristic absorption band at ~1575 cm^{-1} for aromatic ring skeleton, absorption band at ~1379 cm^{-1} for C-N stretching in quinoline ring and absorption band at ~875 cm^{-1} for C-H bending in alkene. Characteristic absorption band observed at ~1630 cm^{-1} for >C=O stretching band, which suggested that the formation of amide with desired substitution. ^{1}H NMR spectra of the compounds showed characteristic signals of all the aromatic proton between 6.00 to 8.00 δppm in all cases, and characteristic singlet signals of all the aliphatic proton between 3.00 to 4.00 δppm in all cases. ^{13}C NMR spectra of compound 5b, 5c and 5g exhibited chemical shift values of carbonyl carbon at 156.28 δppm and chemical shift values of saturated carbon at 52.41 δppm. Signal of methoxy carbon in compound 5g was appeared at 21.45 δppm.

From the results of antimicrobial data, compounds 5e, 5g, 5i, 5j and 5k were shown good activity against bacterial pathogens while compounds 5b, 5c, 5e, 5g, 5i and 5k were found good active against fungi pathogens as compare to the standard drugs. From the results obtained, it could be interpreted that compounds with electron withdrawing group substitution showed moderate activity compared to those possessing electron donating group substitution.

5. CONCLUSIONS

In present report, we submitted very simple, efficient, rapid and scalable method for the synthesis of some new (4-(7-chloroquinolin-4-yl)piperazin-1-yl)(substitutedphenyl) methanone derivatives, All the synthesized compounds were obtained in good to moderate yield. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, Mass, IR spectroscopy and the obtained results are showing good agreement with the synthesized structures. From the results of antimicrobial activity data, compounds 5e, 5k and 5i were shown good activity against bacterial pathogens while compounds 5f, 5c and 5g were found good active against fungi pathogens compare to the standard drugs.

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