Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(22): 94-100
(http://www.derpharmachemica.com/archive.html)

Synthesis, Characterization and Antimicrobial Activity of Some New Substituted Quinoline Hydrazones

Kanu D Katariya, Shailesh R Shah*

Department of Chemistry, Faculty of Science, The MS University of Baroda, Vadodara-390002, India

ABSTRACT

Several 6-bromo-2-methyl-4-(2-(1-phenylethylidene)hydrazinyl) quinolines have been synthesized and characterised by using Infra-Red (IR), Proton nuclear magnetic resonance (^{1}H NMR), Carbon-13 nuclear magnetic resonance (^{13}C NMR) and mass spectral analysis. Their in vitro antimicrobial activities have been evaluated on the pathogenic fungi Fusarium pallidoroseum and Candida albicans and on the Gram-positive bacteria Staphylococcus aureus and Bacillus subtilis and the Gram-negative bacteria Escherichia coli and Pseudomonas aeruginosa. The new bromo quinoline compounds are found to possess a broad spectrum of antimicrobial activities.

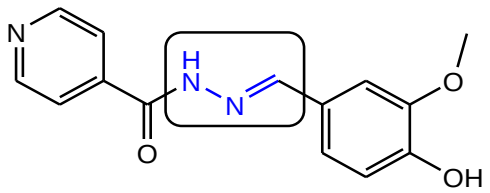
Keywords: 6-Bromo-2-methyl-quinoline, Quinoline hydrazones, Antifungal activity, Antibacterial activity

INTRODUCTION

Quinoline derivatives are widely used as ‘‘parental” components in designing the molecules with medicinal benefits, especially with anti-malarial and anti-microbial activities [1,2]. Quinoline or benzo[b]pyridine is a versatile heterocycle with a wide spectrum of biological activities [3]. Quinoline derived compounds possess anticancer [4,5], antibacterial [6] and antitubercular activities [7,8]. They have also been studied for anti-inflammatory [9,10], anticonvulsant and anti-hypertensive [11] and anti-HIV activities [12].

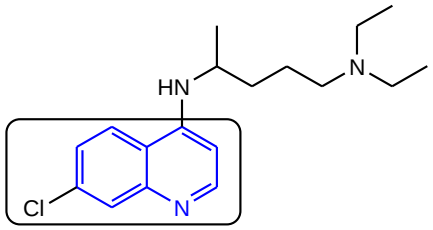
Camptothesin, a quinoline alkaloid shows remarkable anticancer activity [13]. A recent review highlights the anticancer properties of quinoline containing compounds [14].

Hydrazine functionalized quinolines may be utilized to synthesize various quinolyl hydrazones by reacting them with aldehydes or ketones. Hydrazones constitute a class of organic compounds which has attracted the attention of medicinal chemists due to the fact that they possess azomethine (–NH–N=C–) functionality which is responsible for a variety of pharmaceutical applications and can be employed for the synthesis of different heterocyclic scaffolds such as 1, 3, 4-oxadiazolines, azetidin-2-ones, coumarins, 1, 3-thiazolidin-4-ones and 1,3-benzothiazin-4-ones [15]. Hydrazone derivatives are found to possess anti-microbial [16-19], anticonvulsant [20], analgesic [21], anti-inflammatory [22-24], anti-platelet [25], anti-tubercular [26-28] and antitumoral [29-32] activities. Some widely used antibacterial drugs such as furacilin, furazolidone and ftivazide (shown below) contain hydrazone functionality.



Ftivazide

The halogen substituted quinolines are of interest to both synthetic and medicinal chemists as they play a key role in bioactivity of many naturally occurring compounds. Chloro substituted quinolines such as chloroquine (shown below), amodiaquine have been widely used as antimalarial agents.



Chloroquine

The chloro substituted quinolines have been synthesized and widely studied for their biological activity, while bromo substituted quinolines have not been explored or may be considered to be greatly neglected compounds so far.

Looking at the medicinal importance of halogenated and azomethine functionality, some new bromo substituted quinoline 4-hydrazoes have been synthesized, characterized and studied for their antimicrobial activities in the present study. 6-Bromo-2-methyl-quinoline-4-hydrazine was prepared to be transformed into some new quinoline containing hydrazone moieties with either no substitution, nitro substitution or alkyloxy substitution. This resulted in a new series of hydrazones having quinoline as a basic pharmacophoric substructure. The newly synthesized compounds were characterized and were evaluated for antibacterial and antifungal activities against four bacterial and two fungal strains.

MATERIALS AND METHODS

General

All chemicals were of a reliable purity and were used as received. The organic solvents used were distilled and dried following the standard procedures. Column chromatography was carried out using silica gel (60-120 mesh). Thin layer chromatography was performed on pre-coated silica gel 60F254 aluminium sheets. Melting points were determined in open capillaries and are uncorrected. FTIR spectra were recorded on Perkin Elmer FTIR spectrometer between 4000-450 cm-1 in the solid state as KBr discs. The ^{1}H and ^{13}C-NMR spectra were recorded on 400 MHz Bruker instrument and chemical shifts are reported in parts per million downfield from TMS. EI-Mass spectra were recorded on Shimadzu GC-MS spectrometer.

Synthesis of (6-bromo-2-methyl-quinolin-4-yl)-hydrazine (4): The synthesis of the title compound was started with the preparation of 6-bromo-4-hydroxy-2-methyl quinoline (2) which was prepared by heating the mixture of 4-bromoaniline (5.0 g, 53.5 mmol), ethyl acetoacetate (6.96 g, 53.5 mmol) and polyphosphoric acid (25 g, 2.5 w/w) at 150°C for 2 hrs. The product (5 g, 21 mmol) thus obtained was heated with phosphorous oxychloride (20 ml) at 80°C for 4 h after crystallization to yield 4-chloro-2-mehtyl- quinoline (3). Finally (6-bromo-2-methyl-quinolin-4-yl)-hydrazine (4) was obtained following the method reported [33-35] for the other analogues, by the reaction of compound (3) (3 g, 11.7 mmol) and hydrazine hydrate (5 ml) in ethanol (15 ml) at 90°C for 4 h. Yield=57%, Brown solid; mp 169°C; IR (KBr) cm^{-1}: 3241, 3185, 2938, 1639, 1080, 872, 670; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 2.35 (s, 3H, -CH_3), 6.76 (s, 1H, Ar-H), 7.46 (d, J=8.4 Hz, 1H, Ar-H), 7.75 (d, J=8.8 Hz, 1H), 8.10 (d, J=1.2 Hz, 1H Ar-H); ^{13}C-NMR (100 MHz, DMSO-d_6) (δ ppm): 18.6, 107.9, 114.8, 115.1, 119.6, 126.1, 123.1, 124.9, 126.1, 131.1.

Synthesis of 6-bromo-2-methyl-4-(2-(1-phenylethylidene)hydrazinyl)quinoline (7a): An equimolar mixture of acetophenone (0.1 mmol) and (6-bromo-2-methyl-quinolin-4-yl)-hydrazine (0.1 mmol) were dissolved in ethanol (5 ml). A catalytic amount (0.1 ml, 2 drops) of concentrated sulphuric acid was added and the reaction mixture was heated with stirring at 80°C for 4 h, and was then left at room temperature overnight when solid product was separated. The product was filtered, washed with chilled ethanol and crystallized from ethanol-dioxane (1:2) mixture to afford the final compound. Yield (56%); yellow solid; mp 137°C; IR (KBr) cm^{-1}: 3250, 3113, 2939, 1634, 1064, 850, 684; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 2.62 (s, 3H, -N=C-CH_3), 2.74 (s, 3H, qui-CH_3), 7.50 (m, 5H, Ph-H), 7.86 (d, J=8.8Hz, 1H, qui-H), 8.03 (d, J=3.6 Hz, 1H, qui-H), 8.13 (d, J=8.8Hz, 1H, qui-H), 8.99 (s, 1H, qui-H), 11.08 (s, 1H, - qui-NH); ^{13}C-NMR (100 MHz, DMSO-d_6) (δ ppm): 15.7, 20.6, 101.9, 116.3, 119.5, 122.1, 126.4, 127.3, 129.0, 130.8, 136.9, 137.5, 137.6, 151.9, 155.7, 159.1; EI-Mass : m/z $[M]^+$ for $C_{18}H_{16}BrN_3$: 353.03.

Synthesis of 6-Bromo-2-methyl-4-(2-(1-(4-nitrophenyl)-ethylidene)hydrazinyl)quinoline (7b): 4-Nitro acetophenone (0.1 mmol) was reacted with (6-bromo-2-methyl-quinolin-4-yl)-hydrazine (0.1 mmol) following the procedure described above. Yield (83%); yellow solid; mp 143°C; IR (KBr) cm^{-1}: 3078, 2916, 1634, 1597, 1062, 962, 590, 449; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 2.62 (s, 3H, -N=C-CH_3), 2.73 (s, 3H, qui-CH_3), 7.55 (s, 1H, qui-H), 7.82 (d, J=8.8 Hz, 1H, qui-H), 8.11 (d, J=8.8 Hz, 1H, qui-H), 8.26 (2-d, J=8.8 Hz, 4H, Ar-H), 8.95 (s, 1H, qui-H); ^{13}C-NMR (100 MHz, DMSO-d_6) (δ ppm): 15.5, 20.6, 102.6, 116.5, 119.8, 122.1, 124.0, 126.5, 128.5, 136.9, 137.6, 143.6, 148.5, 151.9, 155.7.

Synthesis of 6-Bromo-2-methyl-4-(2-(1-(4-butoxphenyl)-ethylidene)hydrazinyl)quinoline (7c): 4-Butoxy acetophenone (0.1 mmol) was reacted with (6-bromo-2-methyl-quinolin-4-yl)-hydrazine (0.1 mmol) following the procedure described above. Yield (81%); yellow solid; mp 132°C, IR (KBr) cm^{-1}: 3066, 2946, 1638, 1559, 1061, 890, 570, 445; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.93 (t, J=7.6 Hz, 3H, -CH_3), 1.42 (m, 2H, -CH_2), 1.70 (m, 2H, -CH_2), 2.54 (s, 3H, -N=C-CH_3), 2.69 (s, 3H, qui-CH_3), 4.02 (t, J=6.4 Hz, 2H, -OCH_2), 7.01 (d, J=8.8 Hz, 1H, Ar-H), 7.38 (s, 1H, qui-H), 7.7 (d, J=8.8 Hz, qui-H), 7.95 (d, J=8.4 Hz, 2H, Ar-H), 8.08 (d, J=8.8 Hz, 1H, qui-H), 8.91 (s, 1H, qui-H); ^{13}C-NMR (100 MHz, DMSO-d_6) (δ ppm): 14.1, 15.5, 19.1, 20.5, 31.0, 67.8, 101.4, 107.5, 114.8, 116.1, 119.5, 121.9, 126.3, 129.0, 129.6, 130.9, 136.8, 140.8, 151.6, 161.0; EI-Mass: m/z $[M]^+$ for $C_{22}H_{24}BrN_3O$: 425.08.

Synthesis of 6-bromo-2-methyl-4-(2-(1-(4-hexyloxyphenyl)-ethylidene) hydrazinyl) quinoline (7d): 4-Hexyloxy acetophenone (0.1 mmol) was reacted with (6-bromo-2-methyl-quinolin-4-yl)-hydrazine (0.1 mmol) following the procedure described above. Yield (87%); yellow solid; mp 141°C, IR (KBr) cm^{-1}: 2918, 285, 1595, 1550, 1508, 1064, 798, 580; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.89 (t, J=6.8 Hz, 3H, -CH_3), 1.31 (d (br), 4H, -CH_2), 1.41 (m, 2H, -CH_2), 1.74 (m, 2H, -CH_2), 2.57 (s, 3H, -N=C-CH_3), 2.72 (s, 3H, qui-CH_3), 4.04 (t, J=6.4 Hz, 2H, -OCH_2), 7.02 (d, J=8.8 Hz, 2H, Ar-H), 7.42 (s, 1H, qui-H), 7.84 (d, J=8.8 Hz, 1H, qui-H), 7.98 (d, J=8.8 Hz, 2H, Ar-H), 8.12 (dd, J1=8.8 Hz, J2=1.6 Hz,

1H, qui-H), 8.96 (s, 1H, qui-H), 11.08 (s, 1H, -NH); ^{13}C-NMR (100 MHz, DMSO-d_6) (δ ppm): 14.4, 15.5, 20.6, 22.5, 25.6, 29.0, 31.4, 68.1, 101.9, 105.2, 114.8, 116.3, 119.4, 122.1, 126.4, 129.0, 129.6, 131.8, 133.9, 136.8, 151.7, 161.0.

Synthesis of 6-Bromo-4-(2-(1-(4-decylloxy) phenyl) ethylidene)hydrazinyl)-2-methyl quinoline (7e): 4-Decyloxy acetophenone (0.1 mmol) was reacted with (6-bromo-2-methyl-quinolin-4-yl)-hydrazine (0.1 mmol) following the procedure described above. Yield (76%); yellow solid; mp 138°C, IR (KBr) cm^{-1}: 459, 765, 1060, 1106, 1247, 1597, 1634, 2974, 3267; ^{1}H-NMR (400 MHz, DMSO-d_6) (δ ppm): 0.84 (t, J=6.4 Hz 3H, -CH_3), 1.26 (d (br), 12H, -CH_2), 1.39 (d (br), 2H, -CH_2), 1.71 (m, 2H, -CH_2), 2.56 (s, 3H, -N=C-CH_3), 2.71 (s, 3H, qui-CH_3), 4.03 (t, J=6.4 Hz, 2H, -OCH_2), 7.01 (d, J=8.8 Hz, 2H, Ar-H), 7.41 (s, 1H, qui-H), 7.82 (d, J=8.8 Hz, 1H, qui-H), 7.97 (d, J=8.8 Hz, 2H, Ar-H), 8.12 (dd, J1=9.2 Hz, J2=2.0 Hz, 1H, qui-H), 8.94 (s, 1H, qui-H); ^{13}C-NMR (100 MHz, DMSO-d_6) (δ ppm): 14.4, 15.5, 20.5, 22.5, 25.9, 29.0, 29.1, 29.2, 29.3, 29.4, 31.7, 68.1, 114.8, 115.9, 116.3, 118.4, 122.0, 126.3, 129.0, 129.6, 130.4, 130.9, 135.3, 136.7, 151.6, 161.0.

Antibacterial activity

The antibacterial activity of the newly synthesized compounds (7a-e) was studied against four common pathogenic bacterial strains *Staphylococcus aureus*, *Bacillus subtilis* as Gram-positive bacteria and *Escherichia coli* and *Pseudomonas aeruginosa* as Gram-negative bacteria. The studies were carried out using the well-diffusion method [33] by measuring the zone of inhibition. For comparison Ampicillin was taken as the reference drug during the assay. The zone of inhibition was measured in millimetre (mm) scale at two different concentrations (50 and 75 µg/mL) of the compounds.

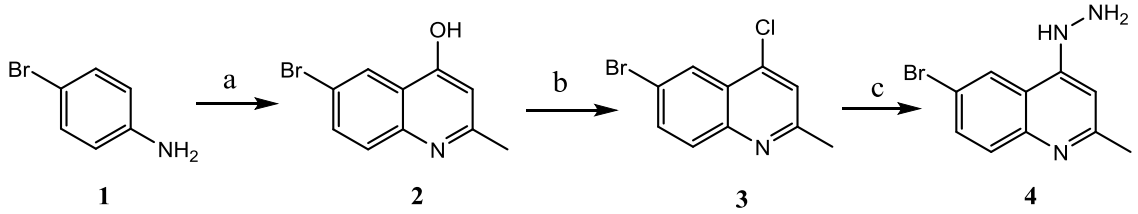
Antifungal activity

The quinolinyl hydrazones (7a-e) were also studied for their antifungal activity by employing standard agar disc diffusion method [34]. The fungi used in this study were *Fusaruim pallidoroseum* and *Candida albicans*. All cultures were maintained on SDA and incubated at 30ºC. To prepare homogeneous suspensions of above fungi for disc assays, they were grown in Savoured broth centrifuged to collect the pellet and buffered saline. The fungal pellet was homogenized in a sterile hand held homogenizer. This suspension was then plated onto SDA using fungal spreader to obtain an even growth field. Sterile 6 mm Whatmann filter paper discs were impregnated with 200 µg/mL concentrations of various test compounds dissolved in Dimethyl Sulphoxide (DMSO) and the reference drug, fluconazole. These discs were then placed at the centre of each quadrant of an SDA plate. Each plate had one control disc impregnated with DMSO. The plates were incubated at 30°C. After 48 h, the plates were removed, and fungal inhibition zone were measured.

RESULT AND DISCUSSION

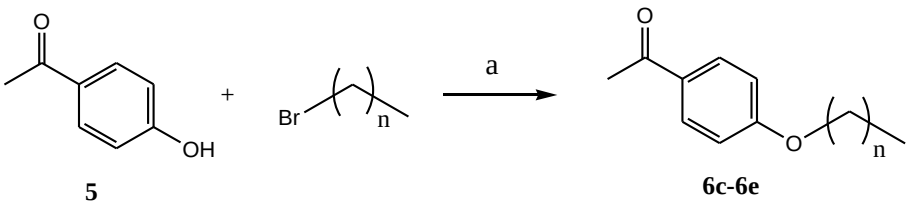
Chemistry

Synthesis of the new chemical entities was initiated from the synthesis of two major starting materials as follows. 6-Bromo quinoline-4-yl hydrazine 4 was prepared from 4-bromoaniline 1 by condensation-cyclization reaction with ethyl acetoacetate using polyphosphoric acid to yield 6-bromo-4-hydroxy-2-methyl quinoline 2 which was then treated with phosphorous oxychloride leading to the 4-chloro quinoline derivative 3 which on heating with hydrazine hydrate gave the required quinoline hydrazine 4 [35] (Scheme-1).



Scheme 1: Reagents and conditions: (a) Ethyl acetoacetate, PPA, 150°C, 2 h; (b) $POCl_3$, 80°C, 4 h; (c) NH_2NH_2. H_2O, ethanol, 90°C, 4 h

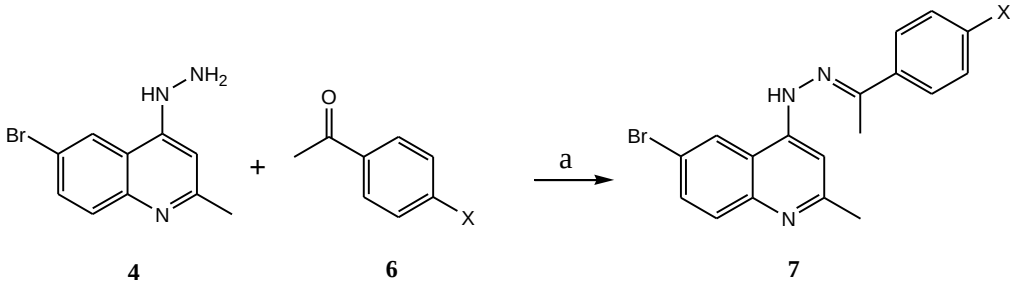
For the preparation of various hydrazones, different aryl ketones were employed. The aromatic ketones selected were un-substituted acetophenone, the acetophenone with an electron withdrawing group, nitro group at para position and the other three with electron donating alkyloxy substitutions. There are many methods reported for the synthesis of 4-alkoxy acetophenones including Friedel-Crafts acylation of alkoxy benzenes. The method employed for the synthesis of medium to long chain 4-alkoxy acetophenones 6c-6e here involved the reaction of 4-hydroxy acetophenone 5 with the corresponding C-4, C-6, and C-10 alkyl bromides in the presence of Potassium Carbonate (K_2CO_3) as a base in Dimethyl Formamide (DMF) as a solvent at 80-90°C [36] (Scheme 2).



n = 3, 5, 9

Scheme 2: Reagents and conditions: (a) DMF, K_2CO_3, 80-90°C, 4h

Final targeted hydrazones 7a-e were obtained in good yield by refluxing equimolar mixture of (6-bromo-2-methyl-quinolin-4-yl)-hydrazine 4 and the acetophenones 6a-6e in the presence of a catalytic amount of concentrated sulphuric acid in ethanol as solvent (Scheme 3). The compounds so obtained were purified by crystallization. Structures, yields and melting points of the final compounds are included in Table 1.

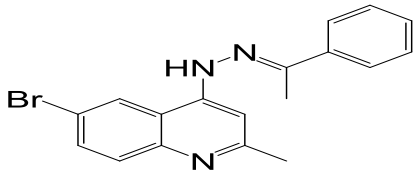
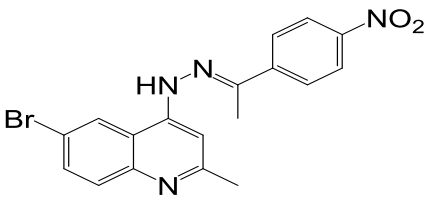
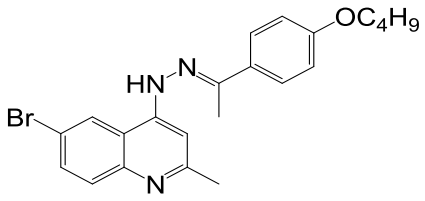
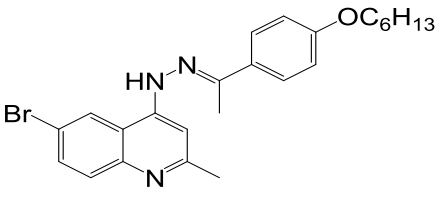
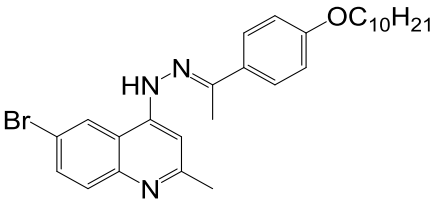


4 **6** **7**

7a X = -H, **7b** X = $-NO_2$, **7c** X = $-OC_4H_9$, **7d** X = $-OC_6H_{13}$, **7e** X = $-OC_{10}H_{21}$

Scheme 3: Reagents and conditions: (a) Ethanol, sulphuric acid, 80°C, 4 h.

Table 1: Structure, yield and melting points of compounds 7a-e

Compound	Structure	% Yield	m.p. (°C)
7a		56 %	137°C
7b		83 %	143°C
7c		81 %	132°C
7d		87 %	141°C
7e		76 %	138°C

Spectral characterization

All the compounds were characterized using IR, ^{1}H NMR, ^{13}C NMR and mass analysis. In IR, a strong band in the frequency range 500-570 cm^{-1} is due to C-Br stretching. While stretching frequency bands at 1550, 1595 cm^{-1} are due to C=C (aromatic) stretching. Bands at 1060 and 1248 cm^{-1} are due to C-O-C stretching of ar-alkyl ether. Stretching band near 1643 cm^{-1} is due to C=N stretching. The Stretching bands at 1388 cm^{-1} and 1535 cm^{-1} showed the presence of $-NO_2$ in compound 7b.

In proton NMR of the quinoline hydrazine the aromatic proton in between hydrazine and methyl groups is seen up field at δ=6.7 ppm while protons on nitrogen were often missing due to moisture in the solvent. In the final compounds, the proton at position 5 of the quinoline moiety is moved down field near δ=9 ppm as a singlet while the other aromatic protons are found in between δ=8.2 to 7.0 ppm. In aliphatic region, two signals are for the methyl group protons, one methyl attached to quinoline ring and the other attached to imine carbon are found near to each other between δ=2.73 to 2.56 as singlets. They have been assigned based on the structure variation and chemical shift value change. For the alkoxy substituted hydrazones $–OCH_2$ protons are seen near δ=4.00 ppm as a triplet while the methyl protons of the alkyl chain are found most upfield near δ=0.9 ppm.

In Carbon-13 NMR the most downfield carbon signal is for hydrazone carbon observed near δ=160 while the other aromatic carbons are observed between δ 152 to 100 and for the alkoxy hydrazones oxygen attached carbon are observed near δ 68 and other aliphatic carbons are observed up field to the solvent (DMSO) signal having chemical shift value up to δ=14 ppm. Mass spectral analysis results show the expected molecular ion peaks for the compounds analysed. Due to presence of bromine, $M:M^{+2}$ mass peaks show equal intensity.

Biological Evaluation

Antibacterial activity studies

Antibacterial activity study of all the new quinoline compounds 7a-e was carried out against *S. aureus*, and *B. subtilis* as Gram-positive bacteria and *E. coli*, and *P. aeruginosa* as Gram-negative bacteria. The results show that all the compounds show very good antibacterial activity (Table 2). Compound 7b possessing nitro group shows remarkable activity against all the four bacterial strains. Compound 7d is showing highest activity against *S. aureus* at the concentration of 75 µg/ml (Table 2 and Figure 1). All the compounds are found to possess excellent activity against *E. coli* at both the concentrations. The compounds also show good activity against *P. aeruginosa* but are less active compared to the activity observed against *E. coli* as reflected in the size of zone of inhibition (Table 2 and Figure 2).

Table 2: Antibacterial activity data of compound 7a-e

Zone of inhibition (mm)								
Compound	**Gram-positive bacteria**				**Gram-negative bacteria**			
	Staphylococcus aureus		***Bacillus subtilis***		***Escherichia coli***		***Pseudomonas aeruginosa***	
Control	0	0	0	0	0	0	0	0
Conc. in µg/ml	75	50	75	50	75	50	75	50
Ampicillin	27	22	31	28	33	26	24	19
7a	17.2	12.3	26.4	19.3	24.3	19.3	17.2	13
7b	25.3	20.4	27.2	26.1	31.3	24.2	20.3	18.5
7c	23.1	18.2	21.6	19.3	29.1	23	21.1	16.4
7d	26	19.1	25.1	22	30.1	21.3	23.2	17.6
7e	24.2	17.1	23.1	21.2	28	22.1	22	16

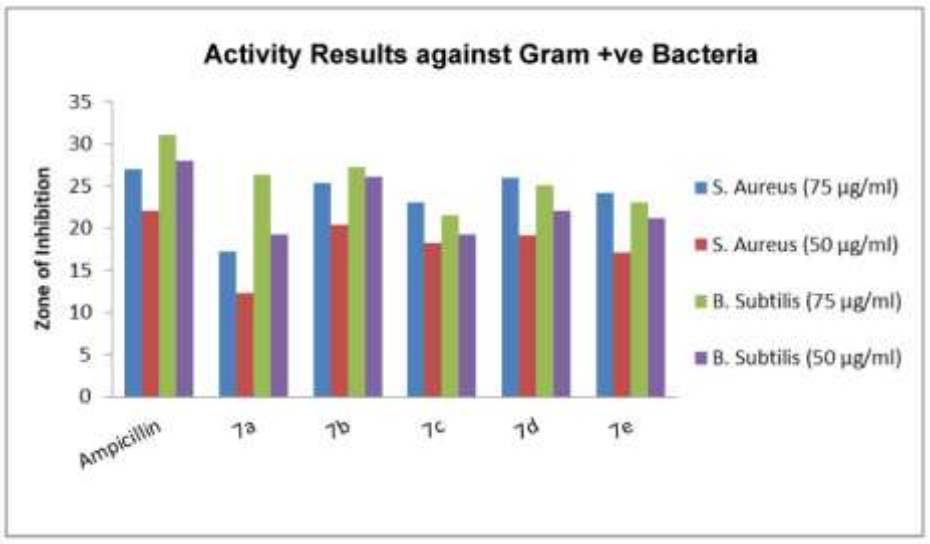


Figure 1: Bar chart projection of antibacterial (Gram-positive) activity of compounds 7a-e

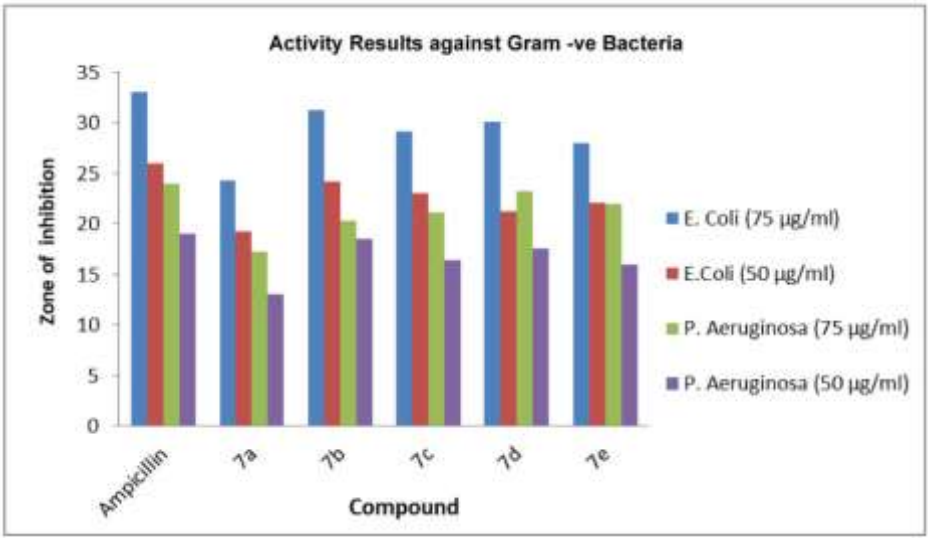


Figure 2: Bar chart projection of antibacterial (Gram-negative) activity of compounds 7a-e

Antifungal activity studies

The antimicrobial activity study was further extended to the study of antifungal activity. The antifungal activity of compounds 7a-e against *F. pallidoroseum* and *C. albicans* was carried out and the zone of inhibition were measured in mm. Compound 7b shows highest potency with 24.0 mm and 25.3 mm zone inhibition against *F. pallidoroseum* and *C. albicans* respectively. Rest of the four compounds show moderate to good potency as shown in the (Table 3 and Figure 3).

Table 3: Antifungal activity data of compound 7a-e

Compounds	Zone of inhibition (mm)	
	Fusarium pallidoroseum	***Candida albicans***
Control	0	0
Fluconazole	26	28
7a	21.6	18
7b	24	25.3
7c	19.2	21.1
7d	20.4	18.5
7e	16.1	14.7

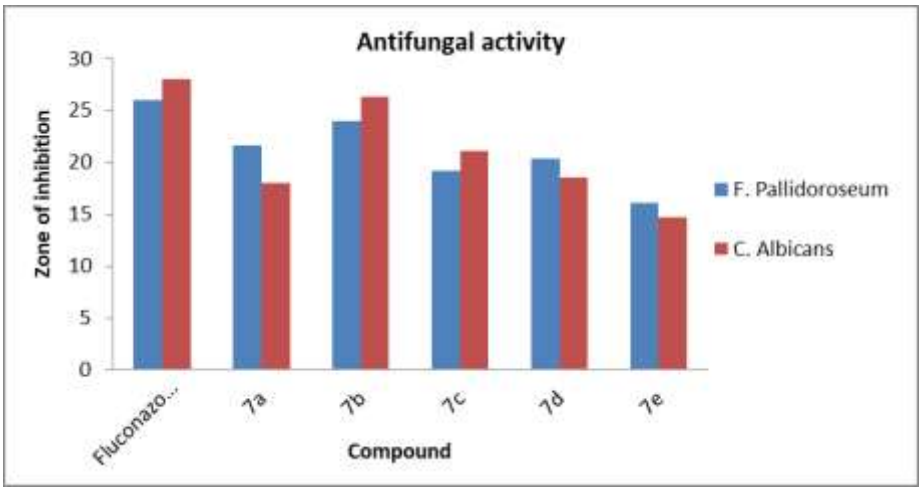


Figure 3: Antifungal activity of compounds 7a-e

CONCLUSION

In conclusion, we have reported here synthesis of some new bromo quinoline hydrazones (7a-e) containing no substitution, nitro substitution and alkyloxy substitutions on the aryl ring derived from the aryl ketones. The final new compounds were studied for antimicrobial activity. All the synthesized compounds show remarkable antibacterial activity. Compound 7b has promising activity against two Gram-positive bacteria and two Gram-negative bacteria with comparable potency as that of the reference antibiotic ampicillin. The same compound was found to have greater

antifungal activity too. Thus the presence of electron withdrawing group in the new quinoline hydrazone compounds is found to contributing in exhibiting higher antimicrobial activity.

ACKNOWLEDGEMENT

400 MHz NMR facility under DST-FIST support and GC-MS facility under UGC-CAS support are gratefully acknowledged. Authors are thankful to the Department of Applied Chemistry, Faculty of Technology and Engineering, The M.S. University of Baroda for IR analysis. UGC New Delhi is acknowledged for the financial support to KDK in form of the project fellowship.

REFERENCES

[1] S. Vandekerckhove, M. D'Hooghe, Bioorg. *Med. Chem.*, **2015**, 23, 5098.
[2] S. Eswaran, A.V. Adhikari, N.S. Shetty, *Eur. J. Med. Chem.*, **2009**, 44, 4637.
[3] A. Marella, O. P. Tanwar, R. Saha, M. R. Ali, *Saudi. Pharm. J.*, **2013**, 21, 1.
[4] J.C. Coa, E. García, M. Carda, R. Agut, I.D. Vélez, J. Muñoz, L. Yepes, S. Robledo, *Eur. J. Med. Chem.*, **2015**, 101, 746.
[5] D.A. Ibrahim, D.A. Abou El Ella, A.M. El-Motwally, R.M. Aly, *Eur. J. Med. Chem.*, **2015**, 102, 115.
[6] S. Eswaran, A.V. Adhikari, I.H. Chowdhury, N.K. Pal, K.D. Thomas, *Eur. J. Med. Chem.*, **2010**, 45, 3374.
[7] A. Lilienkampf, M. Jialin, W. Baojie, W. Yuehong, S.G. Franzblau, A.P. Kozikowski, *J. Med. Chem.*, **2009**, 52, 2109.
[8] B.M. Mistry, S. Jauhari, *Med. Chem. Res.*, **2013**, 22, 647.
[9] S.A.H. El-Feky, Z.K. Abd El-Samii, N.A. Osman, J. Lashine, M.A. Kamel, H.K. Thabet, *Bioorg. Chem.*, **2015**, 58, 104.
[10] P. Mahajan, M. Nikam, A. Asrondkar, A. Bobade, C. Gill, *J. Heterocycl. Chem.*, **2017**, 54, 1415.
[11] N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran, J.T. Leonard, *Biol. Pharm. Bull.*, **2004**, 27, 1683.
[12] N. Ahmed, K.G. Brahmbhatt, S. Sabde, D. Mitra, I.P. Singh, K.K. Bhutani, Bioorg. *Med. Chem.*, **2010**, 18, 2872.
[13] M.E. Wall, M. Wani, C. Cook, K. Palmer, A. McPhail, G. Sim, *J. Am. Chem. Soc.*, **1966**, 88, 3888.
[14] O. Afzal, S. Kumar, R. Ali, R. Kumar, M. Jaggi, S. Bawa, *Eur. J. Med. Chem.*, **2015**, 97, 871.
[15] Ł. Popiołek, *Med. Chem. Res.*, **2017**, 26, 287.
[16] R. Kamal, V. Kumar, V. Bhardwaj, V. Kumar, K.R. Aneja, *Med. Chem. Res.*, **2015**, 24, 2551.
[17] A. Cukurovali, I. Yilmaz, S. Gur, C. Kazaz, *Eur. J. Med. Chem.*, **2006**, 41, 201.
[18] S. Ghiya, Y.C. Joshi, *Med. Chem. Res.*, **2016**, 25, 970.
[19] Y. Özkay, Y. Tunali, H. Karaca, I. Işikdağ, *Eur. J. Med. Chem.*, **2010**, 45, 3293.
[20] J.R. Dimmock, S.C. Vashishtha, J.P. Stables, *Eur. J. Med. Chem.*, **2000**, 35, 241.
[21] P.C. Lima, L.M. Lima, K. Cristine, M. Silva, P. Henrique, O. Léda, A. Luisa, P. De Miranda, C.A.M. Fraga, E.J. Barreiro, *Eur. J. Med. Chem.*, **2000**, 35, 187.
[22] M.A. Abdelgawad, M.B. Labib, M. Abdel-latif, *Bioorg. Chem.*, **2017**, 74, 212.
[23] G. Rajitha, K.V.S.R.G. Prasad, A. Umamaheswari, D. Pradhan, K. Bharathi, *Med. Chem. Res.*, **2014**, 23, 5204.
[24] A.R. Todeschinia, A. Luisa, E. De Miranda, K. Christine, M. Silva, S. Parrinib, E. Barreiro, *Eur. J. Med. Chem.*, **1998**, 33, 189.
[25] G.A. Silva, L.M.M. Costa, F.C.F. Brito, A.L.P. Miranda, E.J. Barreiro, C.A.M. Fraga, *Bioorg. Med. Chem.*, **2004**, 12, 3149.
[26] A. Imramovský, S. Polanc, J. Vinšová, M. Kočevar, J. Jampílek, Z. Rečková, J. Kaustová, *Bioorg. Med. Chem.*, **2007**, 5, 2551.
[27] Y.L. Janin, *Bioorg. Med. Chem.*, **2007**, 15, 2479.
[28] L.C. du Toit, V. Pillay, M.P. Danckwerts, *Respir. Res.*, **2006**, 7, 118.
[29] L. Savini, L. Chiasserini, V. Travagli, C. Pellerano, E. Novellino, S. Cosentino, M.B. Pisano, *Eur. J. Med. Chem.*, **2004**, 39, 113.
[30] M.T. Cocco, C. Congiu, V. Lilliu, V. Onnis, *Bioorg. Med. Chem.*, **2007**, 15, 1867.
[31] N. Ahmed, K. Brahmbhatt, S. Sabde, D. Mitra, I. Singh, K. Bhutani, *Bioorg. Med. Chem.*, **2010**, 18, 2879.
[32] R. Shankar, R.K. Rawal, U. Singh, P. Chaudhary, R. Konwar, K. Hajela, *Med. Chem. Res.*, **2017**, 26, 1459.
[33] M. Balouiri, M. Sadiki, S.K. Ibnsouda, *J. Pharm. Anal.*, **2016**, 6, 71.
[34] S.T. Pai, M.W. Platt, *Lett. Appl. Microbiol.*, **1995**, 20, 14.
[35] W. Luo, W.Q. Lu, K.Q. Cui, Y. Liu, J. Wang, C. Guo, *Med. Chem. Res.*, **2012**, 21, 3073.
[36] V.N. Kozhevnikov, S.J. Cowling, P.B. Karadakov, D.W. Bruce, *J. Mater. Chem.*, **2008**, 18, 1703.