IJPSR (2019), Volume 10, Issue 8 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 November 2018; received in revised form, 27 March 2019; accepted, 01 April 2019; published 01 August 2019

SYNTHESIS AND ANTIBACTERIAL SCREENING OF SCHIFF BASES DERIVED FROM 3-(5-BROMOTHIOPHEN-2-YL)-1-(4-CHLOROPHENYL)-1*H*-PYRAZOLE-4-CARBALDEHYDE

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Keywords:

Hydrazone,
Pyrazole Schiff bases,
Antimicrobial activity

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ABSTRACT: A series of new Schiff bases were synthesized by condensation of 3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde with different aromatic aldehydes. The 3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde was prepared from 1-(1-(5-bromothiophen-2-yl)ethylidene)-2-(4-chlorophenyl)hydrazine by the Vilsmeier Haack reaction. The 1-(1-(5-bromothiophen-2-yl)ethylidene)-2-(4-chlorophenyl) hydrazine was prepared by the condensation reaction of 2-acetyl-5-bromothiophene with 4-chlorophynylhydrazine hydrochloride. The structures of newly synthesized compounds were elucidated by NMR, IR, and Mass spectral - data. Prepared Schiff bases were evaluated for antibacterial activity against four organisms: *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* using streptomycin as a standard drug. Agar well-diffusion method was followed to determine the antimicrobial activity. All prepared Schiff bases showed poor to good activity against test organisms. Based on the zone of inhibition results, it is observed that the newly prepared Schiff bases showed better activity against *Klebsiella pneumoniae* than *Escherichia coli*, *Staphylococcus aureus, and Pseudomonas aeruginosa*. Schiff base 4c showed good activity against *Pseudomonas aeruginosa*, Schiff base 4l showed good activity against *Staphylococcus aureus* and all the Schiff bases 4a-4l except 4c showed good activities against *Klebsiella pneumoniae*.

INTRODUCTION: Heterocyclic compounds have great importance in medicinal chemistry. Pyrazole is an important class of heterocyclic compounds widely used in various areas of chemistry and related sciences.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(8).3741-45

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(8).3741-45

Pyrazole derivatives have attracted much attention of chemists on account of their wide applications in medicinal chemistry.

These compounds show antimicrobial [1-3] anti-inflammatory [4, 5] antitubercular [6], antimalarial [7], insecticidal [8], antifungal [9, 10] and anticancer [11-13] activities. Schiff bases an important scaffold have attracted the interest of chemists due to wide applications in synthetic chemistry and biological point of views. They are also serving as backbone for the synthesis of various heterocyclic compounds.

They are important compounds due to their wide range of pharmacological activities such as antimicrobial [14-20], anticancer [21-22], antifungal [23, 24], anti-inflammatory [25, 26] and DNA- cleavage [27] activities. In the present article, we present the synthesis, characterization and antimicrobial evaluation of Schiff bases prepared from 3-(5-bromothiophen- 2- yl)- 1- (4- chlorophenyl)- 1H-pyrazole-4-carbaldehyde.

MATERIALS AND METHODS: All the chemicals were procured from Sigma Aldrich and SDFINE chemicals and used without further purification. Melting points were determined in open capillary tube and are uncorrected. The progress of the reactions as well as purity of the compounds was monitored by thin layer chromatography with F–252 silica gel precoated aluminum sheets using petroleum ether-ethyl acetate (9:1) as a developing solvent and spots were visualized with near UV and Iodine. The IR spectra were recorded on Shimadzu spectrophotometer using KBr pellets and expressed in cm^{-1}. The NMR spectra were recorded on BRUKER ADVANCE (400 FT-NMR) spectrophotometer in DMSO using tetramethylsilane as an internal standard, and chemical shift values are expressed in δ ppm. The MASS spectra were recorded on Waters UPLC-TQC MASS spectrometer.

Procedure for Preparation of (hydrazone) 1-(1-(5-bromothiophen-2-yl) ethylidene)- 2-(4-chlorophenyl) hydrazine 2: 2-acetyl-5-bromothiophene (0.01 mol), p-chlorophenylhydrazone hydrochloride (0.01 mol) and 2-3 drops of glacial acetic dissolved in 20 ml ethanol. The reaction mixture was stirred on a magnetic stirrer at room temperature for three hours. After the completion of reaction yellow precipitate was obtained, which was filtered, washed and purified by recrystallization with ethanol. Yellow solid, melting point -148 ºC, yield- 70%.

Procedure for Preparation of (Pyrazole) 3-(5-bromothiophen- 2- yl)- 1- (4-chlorophenyl)- 1H-pyrazole-4-carbaldehyde 3: 0.03 mol of $POCl_3$ was added dropwise to an ice-cold solution of 1-(1-(5-bromothiophen-2-yl)ethylidene)- 2-(4-chlorophenyl) hydrazine (3) (0.01 mol) in 10 ml DMF. The reaction mixture was stirred for half an hour at room temperature first and then at 70 ºC for about five hours on a magnetic stirrer. The resulting mixture was poured onto crushed ice and neutralized with a saturated sodium bicarbonate solution. The pale green precipitate obtained was purified by recrystallization with ethanol.

Yellow solid, melting point-158 ºC, yield- 80%, IR (KBr cm^{-1}); 1674 cm^{-1} (C═O), 2785 cm^{-1} (CHO), 3182 cm^{-1} (H--Ar), 1531 cm^{-1} (C═N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 9.9 (s, 1H, CHO), 9.3 (s, 1H, Pyrazole), 7.9 (d, 1H, Ar--H), 7.2 (d, 1H, Ar--H), 7.8 (d, 2H, Ar—H), 7.5(d, 2H, Ar--H). Mass; (M^+) 365, (M^++2) 367.

Procedure for Preparation of Schiff Bases 4a-4l: Equimolar quantities of 3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde 3 (0.01 mol) and different aromatic amines (0.01 mol) and 2-3 drops of glacial acetic were dissolved in 20 ml ethanol. The reaction mixture was refluxed for 3 to 4 h in water bath and cooled at room temperature. Yellow precipitate was obtained which was filtered, washed and purified by recrystallization with ethanol. Physical and Spectral data of representative Schiff bases are as given below.

1- (3- (5- bromothiophen- 2- yl)- 1- (4- chlorophenyl)-1pyrazol-4-yl-Nphenyl methanimine 4a: Yellow solid, yield- 70%, melting point- 118 ºC. IR (KBr, cm^{-1}); 3104 cm^{-1} (H--Ar), 1620 cm^{-1} (HC═N), 1589 cm^{-1} (C═N), 1500 cm^{-1} (C═C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 9.2 (s, 1H, pyrazole), 8.6 (s, 1H, HC═N), 6.9-8.0 (m, 11H, Ar--H). Mass; (M^+) 442.

1-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H- pyrazol- 4- yl)- N- (4- chlorophenyl) methanimine 4b: Yellow solid, yield-85%, melting point-136 ºC. IR (KBr, cm^{-1}); 3140 cm^{-1} (H--Ar), 1612 cm^{-1} (HC═N), 1535 cm^{-1} (C═N), 1500 cm^{-1} (C═C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 9.1 (s, 1H, pyrazole), 8.6 (s, 1H, HC═N), 6.6-8.0 (m, 10H, Ar--H). Mass; (M^+) 478.

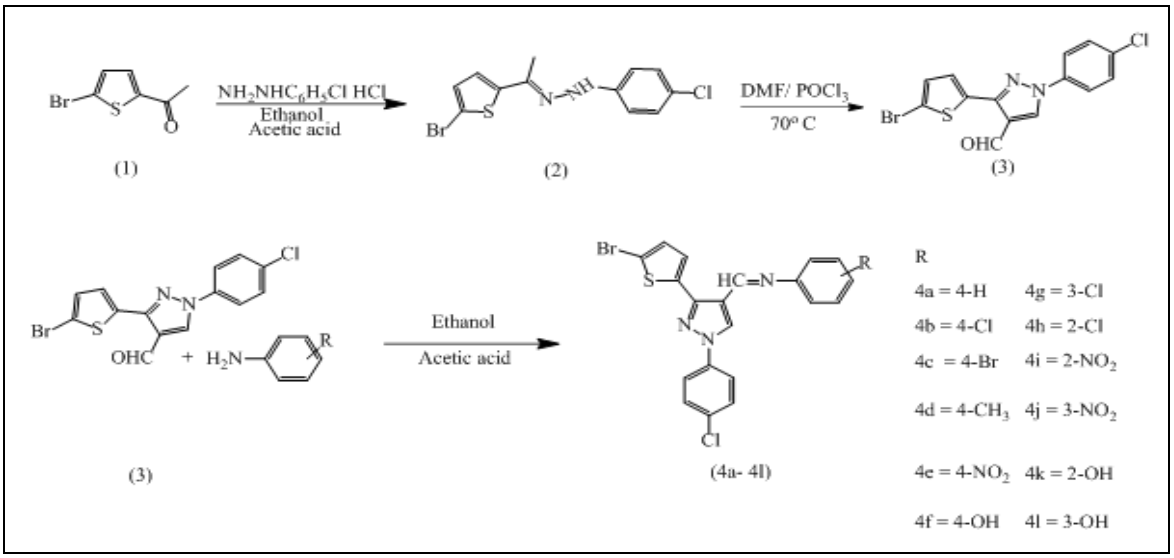
1-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H- pyrazol- 4- yl)- N- (4-bromophenyl) methanimine 4c: Yellow solid, yield-50%, melting point-142 ºC. IR (KBr, cm^{-1}); 3142 cm^{-1} (H--Ar), 1631 cm^{-1} (HC═N), 1539 cm^{-1} (C═N), 1500 cm^{-1} (C═C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 9.4 (s, 1H,

pyrazole), 8.6 (s, 1H, HC═N), 6.5-8.0 (m, 10H, Ar--H). Mass; (M^+) 478.

1- (3- (5- bromothiophen- 2- yl) -1- (4- chlorophenyl)- 1H- pyrazol -4- yl) –N -(p- tolyl) methanimine 3d: Yellow solid, yield-55%, melting point -120 ºC. IR (KBr, cm^{-1}); 3136 cm^{-1} (H--Ar), 1624 cm^{-1} (HC═N), 1597 cm^{-1} (C═N), 1500 cm^{-1} (C═C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 9.1 (s, 1H, pyrazole), 8.6 (s, 1H, HC═N), 2.5 (s, 3H CH_3), 6.4-8.0 (m, 10H, Ar--H). Mass; (M^+) 456.

1-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H- pyrazol- 4- yl)- N- (4-nitrophenyl) methanimine 4e: Yellow solid, yield-50%, melting point-128 ºC. IR (KBr, cm^{-1}); 3128 cm^{-1} (H--Ar), 1631 cm^{-1} (HC═N), 1597 cm^{-1} (C═N), 1527 cm^{-1} (C═C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 9.4 (s, 1H, pyrazole), 8.6 (s, 1H, HC═N), 6.6-8.0 (m, 10H, Ar--H). Mass; (M^+) 489

1-(3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1H-pyrazol-4-yl)-N-(4-hydroxyphenyl) methanimine 4f: Yellow solid, yield-60%, melting point-158 ºC. IR (KBr, cm^{-1}); 3097 cm^{-1} (H--Ar), 1620 cm^{-1} (HC═N), 1546 cm^{-1} (C═N), 1508 cm^{-1} (C═C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 9.1 (s, 1H, pyrazole), 8.6 (s, 1H, HC═N), 6.4-8.0 (m, 10H, Ar--H). Mass; (M^+) 458



SCHEME 1

TABLE 1: ANTIMICROBIAL ACTIVITY OF SCHIFF BASES 4a-4l

Compound	Antibacterial activity (Zone of inhibition in mm)			
	Escherichia coli	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Klebsiella pneumonia*
4a	10	-	**12**	12
4b	-	-	**13**	10
4c	-	10	**14**	-
4d	10	10	**12**	12
4e	12	-	10	10
4f	11	11	11	11
4g	-	10	10	12
4h	-	-	10	11
4i	10	10	11	**14**
4j	12	-	13	12
4k	-	11	11	11
4l	-	**14**	**12**	10
Streptomycin	28	27	27	19

--No activity detectable under experimental condition

Antibacterial Assay: All the synthesized Schiff bases were screened for antimicrobial activity by using four organisms namely *Escherichia coli*, *Staphylococcus aureus, Pseudomonas aeruginosa and Klebsiella pneumoniae* using streptomycin as a standard drug. Agar well-diffusion method was followed to determine the antimicrobial activity. Bacterial cultures were grown in exponential phase

in nutrient broth at 37 ºC for 8 h and adjusted to a final concentration 0.5 McFarland turbidity standard. The nutrient agar plate (thickness 4 to 5 mm) surface is inoculated by spreading a volume of the microbial inoculums over the entire agar surface. A hole with a diameter 6 to 8 mm has punched aseptically with a sterile stainless steel borer. 20 µl of the chemical agent of desired concentration was introduced into the well with the help of micropipette and allowed to diffuse at room temperature for 1 h. The plates were incubated at 37 ºC for 18 h for bacterial pathogens. The diameter of the inhibition zone (mm) was measured with zone reading scale. The antibacterial activity of the synthesized Schiff bases against mention organisms is given in **Table 1**.

RESULTS AND DISCUSSION:

Chemistry: The Schiff bases have been prepared from 3- (5- bromothiophen- 2- yl)- 1- (4-chloro-phenyl)-1H-pyrazole-4-carbaldehyde (3) according to synthetic route as mention in the scheme. Structures of all the compounds were established by IR, ^{1}H-NMR spectroscopy and Mass spectrometry data. The compound1-(1-(5-bromo-thiophen- 2- yl) ethylidene)- 2- (4- chlorophenyl) hydrazine (2) obtained from the reaction between 2- acetyl- 5- bromothiophene and p- chlorophenyl hydrazine hydrochloride. Compound (2) then subjected to Vilseimer-Haack raction to formed 3-(5-bromothiophen-2-yl)- 1- (4- chlorophenyl)- 1H-pyrazole-4-carbaldehyde (3). The formation of compound (3) was confirmed by a sharp signal at 1674 cm^{-1} for C═O stretching and two signals at 2885 cm^{-1} and 1785 cm^{-1} for (H—CO) in the IR spectrum, singlet signal at δ 9.9 ppm for CHO proton and also singlet signal at 9.3 for pyrazolyl proton in the 1H-NMR spectrum.

In the mass spectrum of compound (3) the molecular ion peak was observed at m/z = 365, which corresponds to molecular weight. Schiff bases 4a-4l were formed, when compound (3) was reacted with different aromatic amines in the presence of glacial acetic acid as a catalyst.

The structure of newly synthesized Schiff bases were confirmed by the presence of strong signal at 1620-1635 cm^{-1} in the IR spectrum, the 1H-NMR spectra showed the sharp singlets at δ 9.1-9.4 ppm for pyrazolyl proton and δ 8.6 due to proton of HC═N group of Schiff bases and multiples for aromatic protons are observed in the range of 6.4-8.0 ppm. The m/z values for the characterized Schiff bases obtained are in good agreement with the molecular weights.

Antimicrobial Activity: The results of anti-bacterial screening are shown in **Table 1**. All prepared Sciff bases showed poor to good activity against test organisms. Based on the zone of inhibition results, it is observed that the newly prepared Schiff bases showed better activity against *Klebsiella pneumoniae* than *Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa.* Schiff base 4c showed good activity against *Pseudomonas aeruginosa*, Schiff base 4l showed good activity against *Staphylococcus aureus* and all the Schiff bases 4a-4l except 4c showed good activities against *Klebsiella pneumonia.* Schiff bases 4a-4l showed poor activity against *Escherichia coli.*

CONCLUSION: A new series of Schiff bases were prepared and the structures of newly synthesized Schiff bases were confirmed by IR spectroscopy, 1H-NMR spectroscopy, and Mass spectrometry. These newly prepared Schiff bases showed poor to good activity against the test organisms.

ACKNOWLEDGEMENT: The authors are thankful to SAIF, IISc. Bangalore for ^{1}H-NMR analysis, SAIF, CDRI, Lucknow for Mass analysis and Shri Shivaji Science College, Amravati for IR analysis. One of the authors is grateful to UGC, for the award of teacher fellowship under XII plan of UGC (File no. 29-19/14 WRO.)

CONFLICT OF INTEREST: The authors report no conflict of interest.

REFERENCES:

1. Bekhit AA, Ashour HMA, Ghany YSA, Bekhit AEA and Baraka A: Synthesis and biological evaluation of some thiazolyl and thiadiazolyl derivatives of 1H-pyrazole as anti-inflammatory antimicrobial agents. European Journal of Medicinal Chemistry 2008; 43: 456-63.
2. Rizk HF, Ibrahim SA and El-Borai MA: Synthesis, fastness properties, colour assessment and antibicrobial activity of some azp reactive dyes having pyrazole moiety. Dyes and Pigments 2015: 112: 86-92.
3. Li YR, Chao L, Liu JC, Meng G, Zhang TY, Sun LP, Zheng CJ and Piao HR: Synthesis and biological evaluation of 1,3-diaryl pyrazole derivatives as potential

antibacterial and anti-inflammatory agents. Bioorganic & Medicinal Chemistry Letters 2015; 25(22): 5052-57.
4. Bandga BP, Gawande SS, Bodade RG, Gawande NM and Khobragade CN: Synthesis and biological evaluation of a novel series of pyrazole chalcones as anti-inflammatory, antioxidant and antimicrobial agents. Bioorganic & Medicinal Chemistry 2009; 17: 8168-73.
5. Kumar RS, Arif A, Ahamed A and Idhayadhylla A: Anti-inflammatory and antimicrobial activities of novel pyrazole analogue. Saudi J of Bio Sci 2016; 23(5): 614-20.
6. Castagnolo D, Logu AD, Radi M, Bechi B, Manetti F, Magnani M, Supino S, Meleddu R, Chisu L and Botta M: Synthesis, biological evaluation and SAR study of novel pyrazole analogues as inhibitors of Mycobacterium tuberculosis. Bioorganic & Med Chem 2008; 16: 8587-91.
7. Bekhit AA, Hassan AMM, El-Razik HAA, El-Miligy MMM, El-Agroudy EJ and Bekhit AEA: New heterocyclic hybrids of pyrazole and its bioisosteres: Design, synthesis and biological evaluation as dual acting antimalarial-antileishmanial agents. European Journal of Medicinal Chemistry 2015; 94: 30-44.
8. Hong D, Gang L, Jia C, Yujun S, Shushan G, Chongguang F and Haibing H: Synthesis and biological activities of novel 1,3,4-thiadiazole-containing pyrazole oxime derivatives. Bioorganic & Medicinal Chemistry Letters 2016; 26(15): 3818-21.
9. Sen-Lin W, Yu-Jun S, Hai-Bing H, Yu L, Yang L and Hong D: Synthesis and bioactivity of novel pyrazole oxime derivatives containing oxazole ring: Chinese Chemical Letters 2015; 26 (6): 672-74.
10. Mert S, Kasımogulları R, Tuba ICA, Çolak F, Altun A and Salim OK: Synthesis, structre- activity relationships and *in-vitro* antibacterial and antifungal evaluations of novel pyrazole carboxylic and dicarboxilic acid derivatives. European Journal of Medicinal Chemistry 2014; 78: 86-96.
11. Fahmy HH, Khalifa NM, Ismail MMF, El-Sahrawy HM and Nossier ES: Biological validation of novel polysubstituted pyrazole candidates with *in-vitro* anticancer activities. Molecules 2016; 21: 271. Reddy TS, Kulhari H, Reddy VG, Bansal V, Kamal A and Shukla R: Design, synthesis and biological evaluation of 1,3-diphenyl-1H-pyrazole derivatives containing benzimidazole skeleton as potential anticancer and apoptosis inducing agents. European Journal of Medicinal Chemistry 2015; 101: 790-05.
12. Sankappa RU: Synthesis and *in-vitro* biological evaluation of new pyrazole chalcones and heterocyclic diamides as potential anticancer agents. Arabian Journal of Chemistry 2015; 8(3): 317-321.
13. Chandra S, Gautam S, Rajor HK and Bhatia R: Syntheses, spectroscopic characterization, thermal study, molecular modeling, and biological evaluation of novel Schiff's Base benzil bis(5-amino-1,3,4- thiodiazole-2-thiol) with Ni(II), and Cu(II) metal complexes: Spectrochimica Acta Part A. Molecular and Biomolecular Spectroscopy 2015; 137: 749-60.
14. Mahmoud WH, Deghadi RG and Mohamed GG: Novel Schiff base ligand and its metal complexes with some transition elements. Synthesis, spectroscopic, thermal analysis, antimicrobial and *in-vitro* anticancer activity. Appl Organometal Chem 2016; 30: 221-30.
15. Kalaivani S, Priya NP and Arunachalam S: Schiff bases: facile synthesis, spectral characterization and biocidal studies. International Journal of Applied Biology and Pharmaceutical Technology 2012; 3(1): 219-23.
16. Anacona JR, Noriega N and Camus J: Synthesis, characterization and antibacterial activity of a tridentate Schiff base derived from cephalothin and sulfadiazine, and its transition metal complexes: Spectrochimica Acta Part A. Mol and Biomolecular Spectroscopy 2015; 137: 16-22.
17. Malladi S, Isloor AM, Isloor S, Akhila DS and Fun HK: Synthesis, characterization and antibacterial activity of some new pyrazole based Schiff bases. Arabian Journal of Chemistry 2013; 6: 335-40.
18. Nassar MY, Aly HM, Abdelrahman EA and Moustafa ME: Synthesis, characterization, and biological activity of some novel Schiff bases and their Co(II) and Ni(II) complexes: A new route for CO_3O_4 and NiO nanoparticles for photocatalytic degradation of methylene blue dye. Journal of Molecular Structure 2017; 1143: 462-71.
19. Zayed EM and Zayed MA: Synthesis of novel Schiff's bases of highly potential biological activities and their structure investigation. Spectrochimica Acta Part A. Mol and Biomolecular Spectroscopy 2015; 143: 81-90.
20. Abd-Elzaher MM, Labib AA, Mousa HA, Moustafa SA, Ali MM and El-Rashedy AA: Synthesis, anticancer activity and molecular docking study of Schiff base comp-lexes containing thiazole moiety. Beni- Suef University Journal of Basic and Applied Sciences 2016; 5: 85-96.
21. Shabbir M, Akhter Z, Ahmad I, Ahmed S, Ismail H, Mirza B, McKee V and Bolte M: Synthesis, characterization, biological and electrochemical evaluation of novel ether based ON donor bidentate Schiff bases. Journal of Molecular Structure 2016; 1116: 84-92.
22. Manjunath M, Kulkarni AD, Bagihalli GB, Malladi S and Patil SA: Bioimportant antipyrine derived schiff bases and their transition metal complexes: Synthesis, spectroscopic characterization, antimicrobial, anthelmintic and DNA cleavage investigation. Journal of Molecular Structure 2017; 1127: 314-321.
23. Parmar N, Teraiya S, Patel R, Barad H, Jajda H and Thakkar V: Synthesis, antimicrobial and antioxidant activities of some 5-pyrazolone based Schiff bases: Journal of Saudi Chemical Society 2015; 19 (1): 36-41.
24. Lamie PF, Ali WAM, Bazgier V and Rárová L: Novel N-substituted indole Schiff bases as dual inhibitors of cyclooxygenase-2 and 5-lipoxygenase enzymes: Synthesis, biological activities *in-vitro* and docking study. European Journal of Medicinal Chemistry 2016; 123: 803-13.
25. Rakesh KP, Manukumar HM and Gowda DC: Schiff's bases of quinazolinone derivatives: Synthesis and SAR studies of a novel series of potential anti-inflammatory and antioxidants. Bioorganic & Medicinal Chemistry Letters 2015; 25 (5): 1072-77.
26. Kavitha P, Chary MR, Singavarapu BVVA and Reddy KL: Synthesis, characterization, biological activity and DNA cleavage studies of tridentate Schiff bases and their Co(II) complexes. J of Saudi Chem Society 2016; 20; 69-80.

How to cite this article:
Manohare SV and Thakare SS: Synthesis and antibacterial screening of schiff bases derived from 3-(5-bromothiophen-2-yl)-1-(4-chlorophenyl)-1*H*-pyrazole-4-carbaldehyde. Int J Pharm Sci & Res 2019; 10(8): 3741-45. doi: 10.13040/IJPSR.0975-8232.10(8).3741-45.