Journal of Drug Design and Medicinal Chemistry
2016; 2(4): 35-39
http://www.sciencepublishinggroup.com/j/jddmc
doi: 10.11648/j.jddmc.20160204.11
ISSN: 2472-355X (Print); ISSN: 2472-3576 (Online)

Synthesis and Biological Evaluation of Some New Ferrocenyl Phenyl Guanidines as Antibacterial, Antifungal Agents

Rukhsana Gul[1], Zainab Nawaz[1], Amin Badshah[2, *], Azim Khan[3], Asif Junaid[4], Rabia Naz[5], Muhammad Kamran Rauf[1], Saima Hayat[3]

[1]Department of Chemistry, Kohat University of Science and Technology, Kohat, Pakistan

[2]Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan

[3]Institute of Chemical Sciences, Gomal University, Dera Ismail Khan, Pakistan

[4]Department of Microbiology, Kohat University of Science and Technology, Kohat, Pakistan

[5]Department of Plant Sciences, Quaid-i-Azam University, Islamabad, Pakistan

Email address:

aminbadshah@yahoo.com (A. Badshah)

[*]Corresponding author

To cite this article:

Rukhsana Gul, Zainab Nawaz, Amin Badshah, Azim Khan, Asif Junaid, Rabia Naz, Muhammad Kamran Rauf, Saima Hayat. Synthesis and Biological Evaluation of Some New Ferrocenyl Phenyl Guanidines as Antibacterial, Antifungal Agents. *Journal of Drug Design and Medicinal Chemistry.* Vol. 2, No. 4, 2016, pp. 35-39. doi: 10.11648/j.jddmc.20160204.11

Received: February 29, 2016; **Accepted**: March 29, 2016; **Published**: August 1, 2016

Abstract: A series of new ferrocenylphenylguanidines (d-1 to d-4) were synthesized via multistep protocol. The purity of synthesized compounds were determined by melting point and TLC and their structures were established by various analytical techniques such as elemental analysis, multinuclear (^{1}H and ^{13}C) NMR and FTIR spectroscopy. The newly synthesized compounds were screened for antimicrobial activity against a panel of microorganisms (five bacterial strains, i.e three Gram positive, *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 6538), *Bacillus subtilis* (ATCC 6633) and two Gram negative, *Klebsiella pneumonia* (ATCC 43816), *Escherichia coli* (ATCC 15224) and three fungal strains, i.e. *Fusa rium*m oniliforme, *Aspergillus fumigates* and *Aspergillusflavus*. These compounds were found to have moderate antibacterial and good antifungal activities, especially for compounds having electronegative substituent on phenyl group.

Keywords: Synthesis, Antifungal Activity, Antibacterial Activity

1. Introduction

Guanidine derivatives are of great importance due to their wide presence in the natural products and pharmaceuticals [1, 2]. Many natural occurring metabolites found in varieties of organisms contain guanidine moiety [3]. They have immense applications, especially in the field of medicines as neurotransmitter [6], cardiovascular, antihypertensive drugs [7], antibiotics [8, 9], cytotoxic agents [10] and as an inhibitor of urokinase, responsible for a large number of malignancies including breast, lung, bladder, stomach, cervix, kidney and brain cancers [11-13]. On the other hand, ferrocene is one of the most favored building blocks in the construction of sensing platforms based on redox-active units due to the availability, stability and tailor ability of most of its derivatives [14-16]. Ferrocene and its derivatives have been found to play a vital role in both biological and non-biological systems [17]. Despite the rich chemistry of guanidines as good binding agents and ferrocene as a redox signaling unit, their screening as antimicrobials remained deserted and ferrocenyl guanidine derivatives are barely known and unexplored. Incorporation of phenyl groups on guanidine moiety may decrease the bascicity of guanidines and increase theirlipophylicity and in turn increase the antibacterial and antifungal activies as reported [18]. Introduction of electronegative groups and ferrocene atthe phenyl groupsof N, *N′, N′′*- triphenylguanidinesprovide extended conjugation and further increase in lipophylicity

and an increase in the antimicrobial activities was observed and reported [19]. In the present work the extended delocalization due to ferrocene was decreased by its incorruption at the *meta* position of phenyl ring and the effect on antimicrobial activities was determined.

2. Experimental

2.1. Materials and Methods

Ferrocene, 3-nitroaniline, ammonium thiocyanate, sodium nitrite, hydrochloric acid, benzoic acid, hexadecyltrimetylammonium bromide, palladium on charcoal, hydrazine, thionyl chloride, 4-triflouro methyl aniline, 4-nitroaniline, 4-methyl aniline, 2-methoxy aniline, mercury (II) chloride, were purchased from the local distributer of Fluka, Switzerland. Solvents like acetone, triethylamine, ethanol, dimethylformamide (DMF), diethyl ether and dimethylsulphoxide were bought from Merck Chemicals, Germany. Nitrophenylferrocenes, ferrocenyl anilines and substituted thioureas were made by using the literature methods [20]. All the analytical gradechemicals and solvents were utilized without additional purification. The melting points were recorded on a BioCote SMP10-UK and reported as such. The elemental composition was estimated using LECO-183 elemental analyzer. The solid state FTIR spectrawere recorded on Bio-Rad FTS 3000 MX. ^{13}C and ^{1}H-NMR spectra were recorded on a Bruker-300 MHz spectrometer in $CDCl_3$ using tetra methyl silane (TMS) as an internal reference.

2.2. Synthesis

N-(4-triflourophenyl)-N'-(3-ferrocenylphenyl)-N''-benzoylguanidine (d-1) *N-(4*-triflouromethylphenyl*)-N'*-benzoylthiourea (1.95g, 6mmol) were mixed with the 3-ferrocenyl aniline (1.66g, 6mmol) in 20ml dimethylformamide (DMF) with two equivalents of triethylamine (1.7ml, 12mmol) [19]. Keeping the temperature below 5ºC, Mercuric chloride (1.63g, 6mmol) was added with strong stirring of the reaction mixture. After 30 minutes the temperature was allowed to rise up to room temperature however the stirring continued overnight. The reaction progress was checked by thin-layer chromatography (TLC). The reaction completed with formation of black precipitates of Mercuric sulphide (HgS). Chloroform ($CHCl_3$, 20 ml) was mixed with reaction mixture and HgS residue removed from the reaction mixture with filtration on sintered glass cone. The crude product d-1 was then obtained by the reduced pressure evaporation of solvents from the filtrate. The crude product d-1 was re-dissolved in dichloromethane (CH_2Cl_2, 20 ml) and washed with water (4 x 30 ml). The solvent was evaporated and pure compoundwas re-crystallized from ethanol by slow evaporation (Scheme 1).

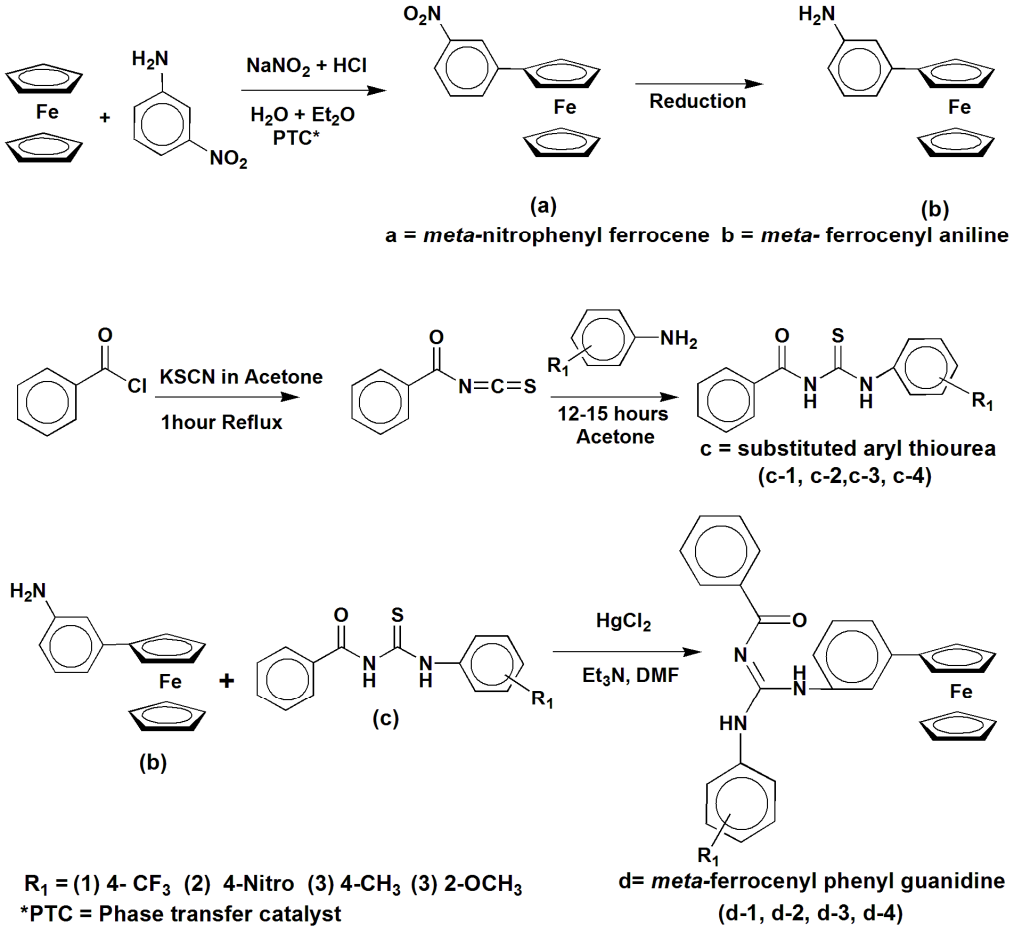

Figure 1. *The reaction scheme for the synthesis of ferrocenyl guanidines (1-4).*

2.2.1. N-(3-ferrocenylphenyl)-N'-(4-triflouromethylphenyl)-N"-benzoylguanidine (d-1)

Yield: 78%; m. p. 158-158.5 °C; FT-IR (KBr, cm^{-1}): 3339.2, 3288.4, 3039.1, 2933.3, 1677.5, 1620.4, 1595.7, 1566.9, 1532.3, 1425.1, 1381.5, 1300.2, 1248.7, 1170.6, 1109.9, 1061.8, 1015.2, 834.5, 630.7, 585.9, 560.1, 525.3, 500.5, 475.2; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.13 (s, 5H, C_5H_5), 4.31 (t, 2H, J = 1.9Hz C_5H_4), 4.89 (t, 2H, J = 1.9Hz C_5H_4), 7.11 (d, H, J = 8.2 Hz, Ar-H), 7.18 (d, H, J = 8.2 Hz, Ar-H), 7.29 (s, H, Ar-H), 7.33 (t, H, J = 8.1 Hz, Ar-H), 7.60 - 8.11 (m, 7H, Ar-H), 8.21 (d, 2H, J = 8.2 Hz, Ar-H), 10.56 (s, H, N-H), 11.61 (s, H, N-H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 67.1 (2C), 67.3 (2C), 67.9 (5C), 84.1, 120.1, 120.7, 121.5, 123.6 (2C), 124.2 (q, J = 3.5 Hz, CF_3), 126.2 (2C), 129.6 (2C), 130.2 (2C), 130.6, 134.7, 135.8, 136.1, 139.8, 141.0, 144.0, 160.3 (CN_3), 179.4(C=O). Anal. Calcd. For $C_{31}H_{24}N_3F_3FeO$ (567.38): C, 65.62; H, 4.26; N, 7.41; Found: C, 65.59; H, 4.25; N, 7.43%;

2.2.2. N-(3-ferrocenylphenyl)-N'-(4-nitrophenyl)-N"-benzoylguanidine (d-2)

Yield: 79%; m. p. 155.5-156.2°C; FT-IR (KBr, cm^{-1}): 3359.9, 3286.7, 3054.8, 2927.1, 1678.3, 1608.5, 1585.7, 1410.9, 1346.2, 1270.4, 1130.6, 1065.8, 1023.1, 1010.3, 893.5, 870.7, 835.9, 590.2, 550.4, 517.6, 495.8, 482.1, 450.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.12 (s, 5H, C_5H_5), 4.33 (t, 2H, J = 1.8Hz, C_5H_4), 4.87 (t, 2H, J = 1.8Hz C_5H_4), 7.2-7.35 (m, 3H, Ar-H), 7.36 (s, H, Ar-H),7.56 (d, 2H, J = 8.1 Hz, Ar-H), 7.60-8.15 (m, 5H, Ar-H), 8.22 (d, 2H, J = 8.1 Hz, Ar-H), 10.52 (s, H, N-H), 11.55 (s, H, N-H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 66.8 (2C), 67.6 (2C), 68.1 (5C), 83.8, 121.1, 121.8, 122.4, 123.5 (2C), 127.5 (2C), 129.3, 129.6 (2C) 130.3 (2C), 130.8, 134.7, 135.2, 135.9, 139.9, 141.8, 160.1 (CN_3), 179.3 (C=O). Anal. Calcd. For $C_{30}H_{24}N_4FeO_3$ (544.3): C, 66.19; H, 4.44; N, 10.29; Found: C, 66.17; H, 4.43; N, 10.31%.

2.2.3. N-(3-ferrocenylphenyl)-N'-(4-methylphenyl)-N"-benzoylguanidine(d-3)

Yield: 76%; m. p. 158.5-159 °C; FT-IR (KBr, cm^{-1}): 3341.2, 3249.4, 3084.6, 3006.8, 1672.3, 1575.5, 1530.7, 1463.9, 1381.1, 1342.8, 1296.4, 1265.7, 1223.8, 1161.3, 1079.2, 1051.4, 1039.6, 935.1, 675.3, 610.2, 566.6, 491.3, 463.6; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, Me-H), 4.11 (s, 5H, C_5H_5), 4.31 (t, 2H, J = 1.9Hz C_5H_4), 4.81 (t, 2H, J = 1.9Hz C_5H_4), 7.12-7.31 (m, 3H, Ar-H), 7.33 (s, H, Ar-H), 7.37 (d, 2H, J = 8.2Hz, Ar-H), 7.45 (d, 2H, J = 8.2Hz, Ar-H), 7.49-7.88 (m, 5H, Ar-H), 10.45 (s, H, N-H), 11.49 (s, H, N-H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 16.1, 66.1 (2C), 67.1 (2C), 67.4 (5C), 82.9, 121.1, 121.4 (2C), 123.3, 123.8 (2C), 128.2, 129.2, 129.6 (2C), 130.1 (2C), 134.3, 134.8, 135.7, 139.9, 140.4, 143.8,156.1 (CN_3), 176.0 (C=O). Anal. Calcd. For $C_{31}H_{27}N_3FeO$ (513.4): C, 72.52; H, 5.30; N, 8.18; Found: C, 72.50; H, 5.29; N, 8.20%.

2.2.4. N-(3-ferrocenylphenyl-N'-(2-methoxylphenyl)-N"-benzoylguanidine (d-4)

Yield: 76%; m.p: 156-158 °C; FT-IR (KBr, cm^{-1}) 3341.8, 3250.5, 3041.4, 2935.2, 1668.5, 1610.6, 1576.8, 1535.2, 1462.7, 1423.4, 1291.8, 1260.6, 1225.3, 1144.6, 1080.7, 1057.5, 1039.4, 1010.6, 895.7, 735.2, 675.5, 608.7, 570.9, 498.1, 465.7, 412.9; ^{1}H NMR (300 MHz, $CDCl_3$): δ3.91 (s, 3H, p-OCH_3), 4.11 (s, 5H, C_5H_5), 4.31 (t, 2H, J = 1.8Hz, C_5H_4), 4.80 (t, 2H, J = 1.8Hz, C_5H_4), 7.11-7.21 (m, 3 H, Ar-H), 7. 28 (s, H, Ar-H), 7.40-7.90 (m, 9H, Ar-H), 10.48 (s, H, N-H), 11.42 (s, H, N-H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 55.4, 66.1 (2C), 67.1 (2C), 67.4 (5C), 82.7, 121.1, 121.5, 123.3, 124.8, 125.3, 126.5, 126.9, 129.1, 129.6 (2C), 130.0 (2C), 133.4, 134.7, 135.9, 139.9, 140.8, 143.0, 159.0 (CN_3), 176.0 (C=O). Anal.Calcd. For $C_{31}H_{27}N_3FeO_2$ (529.4): C, 70.33; H, 5.14; N, 7.94; Found: C, 70.32; H, 5.12; N, 7.95%.

2.3. Antifungal Activity

Compounds (d-1 to d-4) were tested for antifungal activities against *Fusariummoniliforme, Aspergillusflavus and Aspergillus fumigates*. The agar tube dilution protocol was employed as reported [20]. A positive control was made by using pure solvent without the compound and used for comparison purpose. The percentage growth inhibition for all test samples was estimated by using equation (I).

$$\text{Fungal growth Inhibition (\%)} = (1 - A/B) \times 100 \quad \text{(I)}$$

Where A is the linear fungal growth (cm) in the test sample and B is that in control.

2.4. Antibacterial Activity

Antibacterial activities of the synthesized compounds (d-1 to d-4) were tested against five bacterial strains. The disc diffusion method was used to estimate the activity as reported in our previous papers [20]. Pencillin and the free solvent were used as negative and positive controls respectively. The percentage inhibition relative to negative control (penciline) for the tested samples was calculated according to the following equation (II).

$$\text{Bactarial Growth Inhibition (\%)} = 100(X-Y)/(Z-Y) \quad \text{(II)}$$

Where, X, Y and Z is the area of inhibition for test sample.

3. Results and Discussion

The syntheses of the ferrocenylphenylguanidines (d-1 to d-4) were achieved in four steps [19]. In the first step; nitrophenylferrocene (a) was made by the coupling of ferrocene with diazonium salts of corresponding nitroaniline using phase transfer catalyst (CTAB. In next step, the nitrophenylferrocene was converted into ferrocenylaniline (b) by reduction with palladium charcoal and hydrazine. In the third step different substituted thioureas (c-1to c-4) were synthesized by the reaction of substituted aniline with

thiocynates in acetone. In the subsequent step; the benzoylphenylthioureas (d-1 to d-4) were mixed with equimolar ferrocenyl aniline (b) and mercuric chloride in DMF. Two equivalent triethylamine (Et_3N) was used to abstract protons as reported for the synthesis of simple non ferrocenyl guanidines.

The synthesized compounds were characterized in solid along with in solution phase. Elemental analysis as reported in the experimental section shows the sufficient bulk purity of d-1 to d-4. The structure of d-1 to d-4 were established by ^1H &^{13}C NMR spectroscopy. In ^1H-NMR, for compounds d-1 to d-4, there appeared three signals (singlet, triplet and triplet) in the region of 4.14 – 4.89 ppm with the relative integration of (5:2:2) protons. These three signals indicate the presence of mono-substituted ferrocene moiety in the molecular structure. The number of non-aromatic and aromatic protons observed in the specific regions are in agreement with the intact structure of the compounds. In all compounds there appeared abroad singlet with chemical shift value ranging from 10.43 to 11.63 ppm indicates the presence of highly deshielded NH moiety. In ^{13}C-NMR spectra of d-1 to d-4, the most down field carbon signals give the impression in the range of 179.2–180.3 ppm, in literature such kind of signals appeared for carbonyls attached to guanidine nitrogen [18]. The signal, 2nd to the most deshielded carbon, was observed in the range of 160–161 ppm is well known for guanidine carbon (CN_3) reported in literature. In the spectrum of all compounds there observed four singnals in the range of 67–84 ppm indicate the existence of mono-substituted ferrocene. The number of other non-aromatic and aromatic carbons, observed in specific regions, are in agreement with expected structures of d-1 to d-4. So the NMR spectral data confer the intact structure of the molecules in chloroform solution.

In the solid state these compounds were characterized by FTIR spectroscopy. In the FT-IR spectra two peaks, a sharp and a weak, were observed in the range 3366-3239 cm^{-1} those can be assigned to N-H bonds. The C=N stretching band for the test compounds were detected from 1584 to 1598 cm^{-1} demonstrating conjugation between guanidine nitrogen atoms.. A sharp C=O stretch was observed in the range of 1681-1675 cm^{-1}and a characteristic peak for Fe-C associated with the ferrocene group was observed in the range of 447-480 cm^{-1}.

3.1. In-vitro Antifungal Activity

The antifungal activity of the ferrocenylguanidines (d-1 to d-4) against three fungal strains, *Fusariummoniliforme*, *Aspergillus fumigates* and *Aspergillusflavus* were tested using the well diffusion method. The terbinafine was used as a standard drug and the results summarized in Table 1. Compounds d-1 and d-2 showed significant activity against A. flavus and were found good to moderate against F. moniliforme and A. fumigatus.

Table 1. *In-vitro Antifungal assay of the ferrocenylguanidines (d-1 to d-4).*

CompdCode	Percentage inhibition in growth		
	Fusarium moniliforme	***Aspergillus fumigatus***	***Aspergillus flavus***
d-1	61	47	88
d-2	55	17	90
d-3	22	-	21
d-4	22	-	21
PC	92	92	92

PC ¼ terbinafin (1mg/ml) was used as standard drug (positive control), while DMSO
was used as negative control (NC).Zone of inhibition (%).

3.2. In-vitro Antibacterial Activity

All the compounds were tested against three Gram positive, Staphylococcus aureus (ATCC 6538), Pseudomonas aeruginosa (ATCC 6538), Bacillus subtilis (ATCC 6633) and two Gram negative, Klebsiella pneumonia (ATCC 43816), Escherichia coli (ATCC 15224) bacterial strains. Penicillin (1 mg/ml) was used as a standard antibiotic while DMSO solvent as a negative control. The zones of inhibition values in Table 2 represent the mean value of the three readings with standard deviation. Zones of more than 20 mm are characteristic for significant activities, 16-20 mm for good, 14-16 mm for low, and below 14 mm for non-significant activities. The results revealed that compounds d-1 and d-2 show moderate to good activity by comparing with the standard drug. These compounds have been found slightly more active against S. aureus, P. aeruginosa and B. subtilis. However, moderate to low activity against the tested bacteria were found for 3 and 4.

The antifungal and antibacterial results reveal that themolecules having ferrocene at *meta* position show slight less activity as compared to the compounds having ferrocene at the *para* position which may be attributed to decrease in delocalization of lone pair of nitrogen which cause a slight increase in basicity and decrease in lipophilicity. Lipophilic compounds have an easy migration across the lipid membrane of the cell [20].

Table 2. *In vitro antibacterial activity of the ferrocenyl guanidines (d-1 to d-4).*

Compd Code	Percentage inhibition in linear growth				
	S. aureus	***P. aeruginosa***	***B. subtilis***	***K. pneumonia***	***E. coli***
d-1	16.1±0.67	15.1±0.33	15.2±0.88	11.8±0.33	11.1±0.67
d-2	15.2±0.33	15.1±0.67	14.8±0.33	12.2±0.58	11.2±0.33
d-3	13.1±0.58	12.8±0.67	11.1±0.33	10.2±0.33	10.3±0.33
d-4	12.5±0.67	12.3±0.33	12.1±0.33	11.0±0.67	10.1±0.58
PC	26.7±0.33	26.3±0.33	27.3±0.67	23.0±0.58	20.3±0.67

PC ¼ penicillin (1 mg/ml) was used as standard drug (positive control), while DMSO was used as negative control.
a Zone of inhibition in mm

4. Conclusion

The present work described the synthesis of four new ferrocenylguanidines (d-1 to d-4) and were characterized in good yields. These compounds were highly pure as characterized by different spectroscopic techniquesin solid state as well as in solution phase. The antibacterial and antifungal studies showed that these compounds have moderate to low antibacterial activities, whereas compounds 1 and 2 have shown significant antifungal activity against *A. flavus* and were found moderately active against *F. moniliforme* and *A. fumigatus*. The antifungal and antibacterial results reveal that the molecules having ferrocene at *meta* position show slight less activity as compared to the compounds having ferrocene at the *para* position which were reported earlier. The preliminary antifungal screening data of these compounds against *A. flavus* demonstrate these as potent candidates for the effective control of such pathogens.

References

[1] Clark, J. F.; Guanidino Compounds in Biology and Medicine, *Springer US, New York*, 2003.

[2] Heys, L. Moore, C. G. Murphy, P. J. *Chemical Society Reviews*. 1999, 29, 57-67.

[3] Berlinck, R.G.S. *Natural Product Reports*. 1999, 16, 339-365.

[4] Yamamoto, Y. Kojima, S. Patai, S. Rappoport, Z. *The Chemistry of Amidines and Imidates*, *John Wiley & Sons, New York*, 1991.

[5] Anslyn, E. V. Bacher, A. Eisenreich, W. Dugas H. *Bioorganic Chemistry Frontiers, Springer-Verlag GmbH*, 1993.

[6] Weiss, S. Keller, M. Brenhardt, G. Buschauer, A. Keoing, B. *Bioorganic Medicinal Chemistry*. 2010, 18, 6292-6304.

[7] Piller, L. B. Davis, B. R. Cutler, J. A. *Current Controlled Trials in Cardiovascular Medicine*, 2002, 3, 1-9.

[8] Heaslet, H. Harris, M. Fahnoe, K. Sarver, R. Putz, H. Chang, J. Subramanyam, C. Barreiro, G. *Bioinformatics*,2009, 76, 706-717.

[9] Zhu, M. Burman, W.J. Jaresko, G. S. Berning, S. E. Jelliffe, R.W. Peloquin, C.A. *Pharmacotherapy*, 2001, 21, 1037-1045.

[10] Fresneda, P. M. Delgado, S .Francesch, A. Manzanares, I. Cuevas, C. Molina, P. *Journal of Medicinal Chemistry,* 2006,49, 1217-1221.

[11] Meurling, L. Marques, M. Nilsson, S. Holmberg, A.R. *International Journal of Oncology*. 2009, 35,281-285.

[12] Li, S. L. Huang, C. H. Lin, C. C. Huang, Z. N. Chern, J. H. Lien, H.Y. Wu, Y. Y. Cheng, C. H. Chang, C. Y. Chuu, J. J. *Investigational New Drugs*,2011,29, 195-206.

[13] Brzozowski, Z. *European Journal of Medicinal Chemistry*, 2002, 37, 285-293.

[14] Peckham, T. J. Elipe, P. G. Manners, I. Togni, A. Halterman, R.L. Metallocenes: Synthesis, Reactivity, Applications, vol. 2, *Wiley-VCH, Weinheim*, 1998.

[15] Forgues, S. F. Nicot, B. D. *Journal of Photochemistry and Photobiology. A. Chem*. 2000, 132, 137-159.

[16] Nguyen, P. Elipe, P. G. Manners, I. *Chemical. Reviews,* 1999, 99, 1515-1548.

[17] Lal, B. Badshah, A. Altaf, A. A. Khan, N. Ullah, S. Applied Organometallic Chemistry. 2011, 25, 843-855.

[18] Murtaza, G. Rauf, M. K. Badshah, A. Ebihara, M. Said, M. Gielen, M. De Vos, D. Dilshad, E. Mirza, B. *European Journal of Medicinal Chemistry*, 2012, 48, 26-35

[19] Gul R, Altaf A. A, Khan A, Badshah A, Shah A, Rehman ZU, Naz R, Tahir MN, Junaid A. Biologically Active New N, N', N"-Tri-Substituted Ferrocenyl Phenylguanidines and their Characterization. *Medicinal Chemistry*. 2016 Jan 28 [Epub ahead of print].

[20] Gul, R. Rauf, M. K. Badshah, A. Azam, S. S. Tahir, M. N. Khan, A. *European Journal of Medicinal Chemistry*, 2014, 85, 438-449.