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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, antibacterial screening, and POM analyses of novel bis-isoxazolyl/pyrazolyl-1,3-diols

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Abstract This research article reports the synthesis of 4,6-bis(5-aryl/heteroaryl-1,2-oxazol-3-yl)benzene-1,3-diol **4a–4f** and 4,6-bis(5-aryl/heteroaryl-1*H*-pyrazol-3-yl)benzene-1,3-diol **5a–5f** from 1,1′-(4,6-dihydroxybenzene-1,3-diyl)bis(3-aryl/heteroarylpropane-1,3-dione) **3a–3f**. The compounds were fully characterized using spectroscopic analyses and tested for their antibacterial activity. A correlation of structure and activities relationship of these compounds with respect to molecular modeling, Lipinski rule of five, drug likeness, toxicity profiles, and other physico-chemical properties of drugs are described and verified experimentally.

Keywords Bis-isoxazole/pyrazole derivatives · Antibacterial activity · Virtual screening · Petra, Osiris, Molinspiration (POM) · Bioinformatics

Introduction

The increasing antimicrobial and multiple resistances have resulted in increasing difficulties in the treatment of bacterial infections. Resistance leads to inappropriate empirical therapy, delay in starting effective treatment, and the use of less effective, more toxic, and more expensive drugs. Although studies are not always consistent, antimicrobial resistance in the infecting organisms is associated with treatment failure, prolonged or additional hospitalization, increased costs of care, and increased mortality. Additional costs and lost bed days are incurred by the need to control the spread of antimicrobial-resistant organisms within hospitals. All this has significant direct impact on patients and their families and also secondary effects on the cost effectiveness of healthcare delivery. Hence, there is a foremost urgent need to control antimicrobial resistance by preparing improved antibiotic drugs.

This work reports the synthesis, antimicrobial activity, and POM analyses of bis-isoxazole/pyrazole derivatives. Pyrazoles and isoxazoles; and their variously substituted derivatives are important biological agents and a significant amount of research activity has been directed toward this class. A numerous reports have appeared in the literature, which highlighted their chemistry and use. Pyrazole derivatives, in particular, are used as an antitumor (Taylor *et al.*, 1992), antibacterial and antifungal, antiviral, antiparasitic, anti-tubercular, and insecticidal agents (Abdel-Rahman *et al.*, 2007; Bhat *et al.*, 2005; Holla *et al.*, 2000; Maggio *et al.*, 2001; Michael *et al.*, 1990; Sharshira and Hamada, 2011; Rashad *et al.*, 2005, 2008). Some of these compounds also have anti-inflammatory, anti-diabetic, anesthetic, and analgesic properties (Clinton *et al.*, 1959; Urmila *et al.*, 2005; Vibhute and Basser, 2003). In similar way, the isoxazole nucleus is well known for its medicinal importance and a number of related compounds are known to exhibit antifungal (Santos *et al.*, 2010), antimicrobial (Ravi *et al.*, 2009), anticancer (Kamal *et al.*, 2010), analgesic, anti-inflammatory (Jayashankar *et al.*, 2009), antituberculine (Kini *et al.*, 2009), antiviral (Mazzei *et al.*,

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1993), antipsychotic (Barceló *et al.*, 2007), and hypoglycemic (Kumar *et al.*, 2009) activities.

In appraisal of the aforementioned facts we describe herein the synthesis of some new bis-pyrazole and bis-isoxazole derivatives bearing 1,2-dihydroxyphenyl moiety in a goal to get some new more active antimicrobial agents (Fig. 1).

Results and discussion

Chemistry

In this study six of each bis-isoxazole and bis-pyrazole derivatives have been prepared and evaluated for their antimicrobial activity.

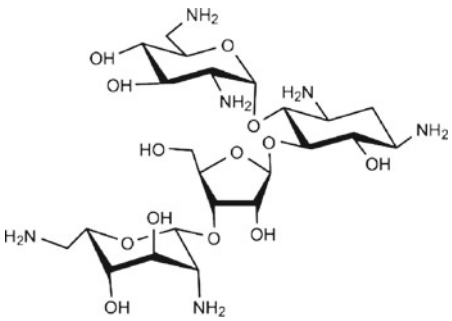
In first step, 1,3-diaroyloxy/heteroaroyloxy-4,6-diacetylbenzene **2a**–**2f** were prepared from 4,6-diacetylresorcinol **1**. In second step, 1,1′-(4,6-dihydroxybenzene-1,3-diyl)bis(3-aryl/heteroarylpropane-1,3-dione) **3a**–**3f** were obtained by base catalyzed Baker–Venkataraman transformation of **2a**–**2f**. Bis-isoxazoles **4a**–**4f** and bis-pyrazoles **5a**–**5f** have been achieved by interaction of **3a**–**3f** with hydroxylamine hydrochloride and hydrazine hydrate in presence of KOH in ethanol, respectively (Scheme 1).

Spectral studies of **4a**–**4f** and **5a**–**5f**

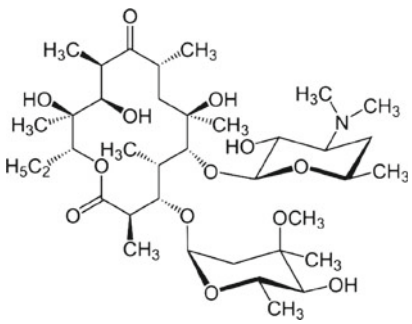
The synthesized bis-isoxazole and bis-pyrazole derivatives were characterized by FTIR, ^{1}H-NMR, ^{13}C-NMR, and Mass spectroscopic analysis. All the compounds were obtained in good to excellent yield.

In IR spectra of 4,6-bis(5-aryl/heteroaryl-1,2-oxazol-3-yl)benzene-1,3-diol (**4a**–**4f**), the stretching frequency from 3,406 to 3,597 cm^{-1} corresponds to the presence of phenolic-OH in the skeleton. The presence of C=N and C–O stretch was shown by the bands at 1,631–1,656 and 1,412–1,452 cm^{-1}, respectively. The IR spectra of these compounds reveal a characteristic aromatic stretch at 2,925–3,119 cm^{-1}. Similarly, in IR spectra of 4,6-bis(5-aryl/heteroaryl-1*H*-pyrazol-3-yl)benzene-1,3-diol (**5a**–**5f**), the stretching frequency from 3,412 to 3,557 cm^{-1} corresponds to the presence of phenolic-OH in the skeleton. The presence of C=N and C–N stretch was shown by the bands at 1,629–1,666 and 1,425–1,460 cm^{-1}, respectively. The IR spectra of these compounds reveal a characteristic aromatic stretch at 2,950–3,153 cm^{-1}. In both, bis-isoxazole and bis-pyrazole derivatives C=O stretch is absent. All other peaks in the spectra are in well agreement with the contents of functionalities in the synthesized **4a**–**4f** and **5a**–**5f** compounds.

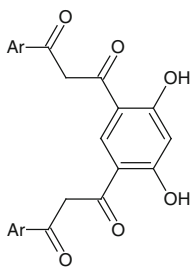
The ^{1}H NMR spectra were recorded in DMSO-d_6 at room temperature using TMS as internal standard. The ^{1}H NMR data of compounds **4a**–**4f** and **5a**–**5f** reveal multiplet peaks between 6.32 and 8.73 ppm owing to the presence of aromatic protons. The absence of enolic proton at 15.89–15.99 ppm and existence of Ar–OH peak at 5.21–5.46 ppm rather than at 12.01–12.11 ppm as in ^{1}H NMR spectra of **3a**–**3f** are in complete agreement with the



Neomycin



Erythromycin



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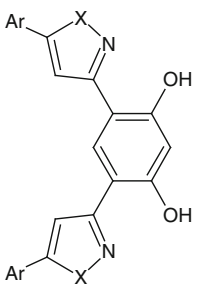
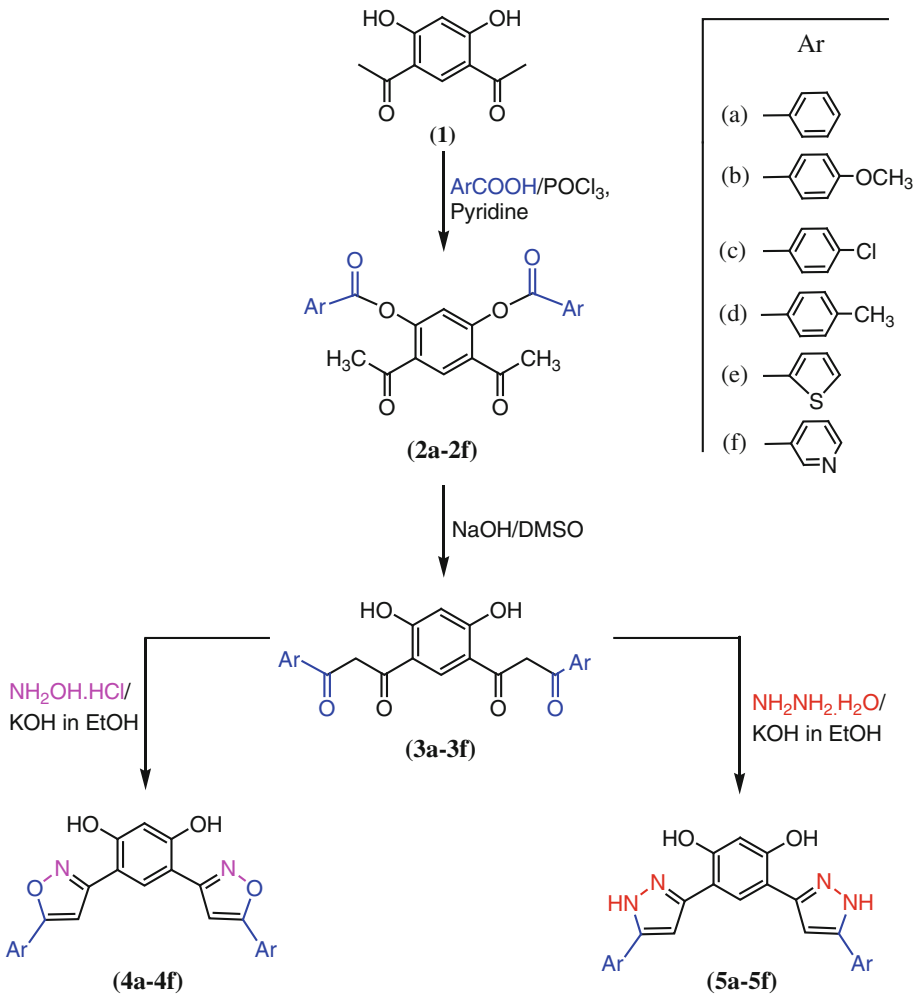


4 (X = O); **5** (X =NH)

Fig. 1 Chemical structure of clinical standard drugs and candidates **3**–**5**



Scheme 1 Synthesis of 4, 6-bis(5-aryl/heteroaryl-1, 2-oxazol-3-yl)benzene-1,3-diol **4a–4f** and 4,6-bis(5-aryl/heteroaryl-1*H*-pyrazol-3-yl)benzene-1,3-diol **5a–5f**

assigned structure of **4a–4f** and **5a–5f**. All the compounds have given the satisfactory elemental analysis.

Antibacterial activity of compounds 3–5

The antibacterial activities of the compounds **4a–4f** and **5a–5f** were carried out against some strain of bacteria as mentioned in the method. The test results presented in Table 1 suggest that compounds **4b**, **4c**, **4f**, **5a**, **5c**, and **5f** are found active against all the bacterial strain. Most of the compounds are found active against two of the four strains.

The excellent antibacterial activity of **4b**, **4c**, **5a**, and **5c** compounds is due to the substituents bearing electro-withdrawing groups. The increased activity of **4f** and **5f** compounds is due to the introduction of nitrogen atom (pyridyl ring) in the bis-pyrazole and bis-isoxazole derivatives.

Modern drug discovery is largely based on screening of small molecules against macromolecular disease targets requiring molecular screening libraries of drug-like or lead-like compounds. Various investigators have used computational methods in understanding efficacy and efficiency of natural products and other sources of drug leads. We have analyzed known standard references (neomycin and erythromycin) for drug-like and lead-like properties which would establish a strategy in designing specific drug-like or lead-like armed bis-isoxazole/bis-pyrazole products.

Tautomerism is an important and under-appreciated phenomenon in the drug design process. Therefore, the purpose of this study is important and has a potential to improve how the descriptor-based QSAR studies are performed. So, we have to avoid choosing a simplistic approach to the problem. Tautomer equilibria in homologous structures depend on structure and the fractions of individual tautomers in the equilibrium mixture will vary from compound to compound in the set. These fractions are a key component in the correct correlation equation. The fractions can be obtained using publicly available resources, e.g., SPARC web server. It has been shown (Natesan *et al.*, 2012) that the drug-receptor binding constant is the sum of the binding constants for individual tautomers

Table 1 Antibacterial activity of compounds **3–5**. Minimum inhibitory concentration (MICs, mg mL^{-1})

Compounds	Aryl	Gram-positive		Gram-negative	
		M. albus	*B. substilis*	*E. coli*	*P. vulgaris*
3a	Ph	15.15	15.78	12.45	13.30
3b	4-CH_3O-Ph	16.12	14.90	11.40	–
3c	4-Cl-Ph	14.98	13.23	–	10.99
3d	4-CH_3-Ph	13.14	16.24	13.75	12.55
3e	2-Thiophenyl	14.95	15.54	15.50	14.90
3f	3-Pyridyl	15.67	11.90	16.45	14.25
4a	Ph	–	11.23	16.98	15.25
4b	4-CH_3O-Ph	15.87	16.48	14.33	15.45
4c	4-Cl-Ph	15.03	13.65	12.66	13.25
4d	4-CH_3-Ph	14.65	12.66	–	11.43
4e	2-Thiophenyl	15.98	13.21	12.50	–
4f	3-Pyridyl	16.09	15.75	12.44	11.9
5a	Ph	13.98	12.25	15.19	15.24
5b	4-CH_3O-Ph	14.40	15. 54	12.12	–
5c	4-Cl-Ph	15.66	16.25	15.03	15.74
5d	4-CH_3-Ph	–	12.45	14.65	15.68
5e	2-Thiophenyl	11.65	–	15.36	15.29
5f	3-Pyridyl	15.28	14.20	15.19	15.44
Neomycin	–	25.78	26.12	26.12	25.29
Erythromycin	–	26.11	27.12	27.45	25.10

Diameter of inhibition zone in mm; (–): no zone of inhibition

multiplied by the fractions of individual tautomers. This makes the correlation equation nonlinear in coefficients so a nonlinear regression technique must be used to optimize the coefficients. Although more complicated than the use of linear techniques, this is the price of treating the system with a realistic approach. The used data sets contain cell-level bioactivities, so the intracellular disposition also needs to be considered. So we suggest that the study is re-worked with the multi-species formalism (Fig. 2). The "Tauto-01" is attributed to the most predominant and stable tautomeric form of series **3–5**.

POM analyses of compounds 3–5

Petra/Osiris/Molinspiration analysis (POM) is one of the well-known approaches that have been used regularly to produce the two dimensional models to identify, and to indicate the type of pharmacophore site that affects biological activity with a change in the chemical substitution (Alafeefy *et al.*, 2012; Chohan *et al.*, 2010; Hadda *et al.*, 2012a, b, c, d; Jarrahpour *et al.*, 2012; Mahajan *et al.*, 2012; Masand *et al.*, 2012; Ozcelik *et al.*, 2013; Parvez *et al.*, 2010; Sheikh *et al.*, 2011; Sheikh and Hadda, 2013). The advantages of POM are the ability to predict the biological activities of the molecules and to represent the relationships between steric/electrostatic property as well as biological activity in the form of pharmacophore site, which gives key features on not only the ligand–receptor interaction but also on the topology of the receptor (Alafeefy *et al.*, 2012; Chohan *et al.*, 2010; Hadda *et al.*, 2012a, b, c, d; Jarrahpour *et al.*, 2012; Mahajan *et al.*, 2012; Masand *et al.*, 2012; Ozcelik *et al.*, 2013; Parvez *et al.*, 2010; Sheikh *et al.*, 2011; Sheikh and Hadda, 2013). Hence to find out the structural features for the bacteria inhibitory activity, we have carried out POM analysis of series **3–5**.

Osiris calculations

Structure-based design is now fairly routine but many potential drugs fail to reach the clinic because of ADMET liabilities. One very important class of enzymes responsible for many ADMET problems is the cytochromes P450. Inhibition of these or production of unwanted metabolites can result in many adverse drug reactions. To assess the possible toxicity risks associated with **3–5**, Osiris a freely available online program was used (Htskuldsson, 1988).

Molinspiration calculations

CLogP (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment based contributions and correction factors

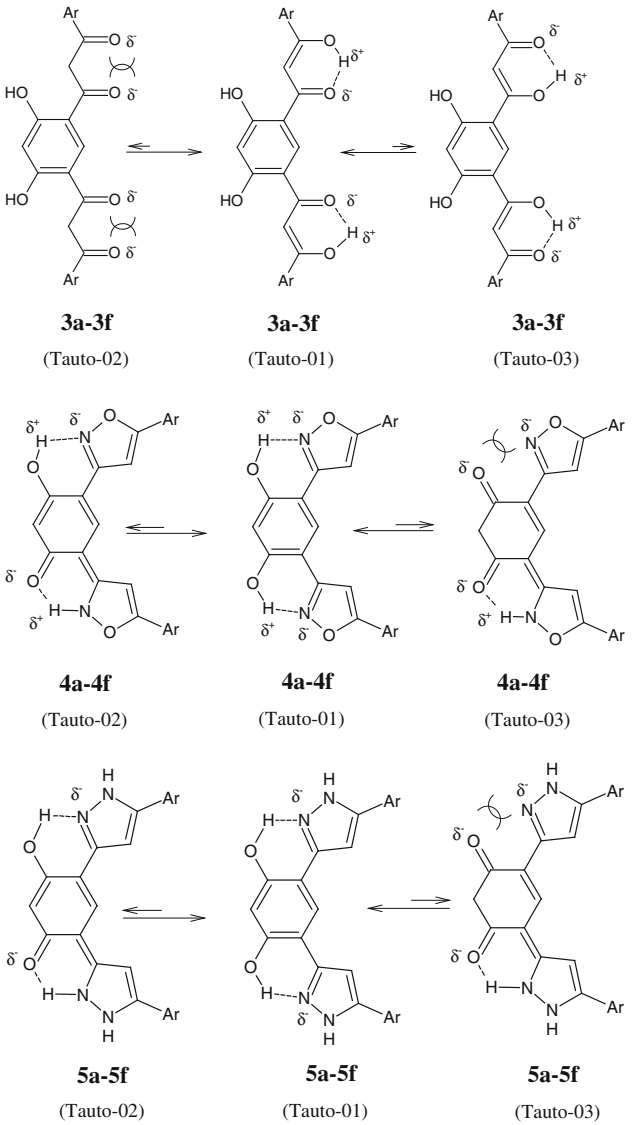


Fig. 2 Chemical structure of most important tautomers of **3–5**

(Table 2). The method is very robust and is able to process practically all organic and most organometallic molecules. Molecular polar surface area TPSA is calculated based on the methodology published by Ertl *et al.* (2000) as a sum of fragment contributions. O– and N– centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability, and blood–brain barrier penetration. Prediction results of compounds **3–5** molecular properties (TPSA, GPCR ligand, and ICM) are valued (Table 3).

Conclusion

This work provided us with structure–activity and structure–cytotoxicity information of a novel bis-isoxazolyl/pyrazolyl-1,3-diols (BISOD) family. Indeed, this study proved that a simple control of nature of few numbers of substitutions leads to compounds with encouraging activities against both Gram positive and Gram negative bacteria with reduced cytotoxicities.

POM analyses of the BISOD compounds **3–5** showed that lipophilic substituents bearing electro-withdrawing groups could be introduced in benzene-1,3-diol moiety maintaining a good antibacterial activity. Introduction of nitrogen atom (1-*H*-pyrazol-3-yl) instead of oxygen atom (1-oxazol-3-yl) on the BISOD template provided three additional compounds **5a–5f** with similar antibacterial activity. The BISOD-molecules bearing ($NH^{\delta+}/O^{\delta-}$) and ($N^{\delta-}/HO^{\delta+}$) pharmacophore sites in equilibrium constitute potential antibacterial drugs.

Experimental

Materials and methods

The solvents and reagents used in the synthetic work were of analytical grade obtained from Qualigens India and were purified by distillation or crystallization where necessary and their boiling or melting points were compared with the available literature values. Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Perkin Elmer FTNMR Cryo-magnet Spectrometer 400 MHz (Bruker) instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as a solvent. Chemical shifts are given in parts per million (ppm). Infrared spectra were recorded on Shimadzu-IR Prestige 21. Mass spectra were recorded on a Waters Micro Mass Q–T of Micro Spectrometer. The reactions were monitored and the purity of products was checked on precoated TLC plates (silica gel 60 F254, Merck), visualizing the spots under ultraviolet light and iodine chamber. The purifying and drying of compounds and solvents were done by usual process.

General procedure for the synthesis of compounds **2–5**

*General procedure for the preparation of 1,3-diaroyloxy/heteroaroyloxy-4,6-diacetylbenzene **2a–2f***

4,6-Diacetylresorcinol (**1**) (0.1 mol) and aromatic carboxylic acids (0.02 mol) were dissolved in 5 mL of redistilled pyridine and cooled, to that $POCl_3$ 1 mL was added dropwise with constant stirring maintaining the temperature below 20 °C. The reaction mixture was kept overnight at room temperature and poured with stirring on ice cold diluted HCl (1 mol in 50 mL). A white granulated solid compound **2** separated out which was washed with cold

Table 2 Osiris calculations of compounds **3–5**

Compounds	MW	Toxicity risk				Osiris calculations			
		MUT	TUMO	IRRI	REP	CLP	S	D-L	D-S
3a	402	+++	+++	++	+++	3.00	−4.54	−0.62	0.36
3b	462	++	+++	++	+++	2.79	−4.57	−0.35	0.28
3c	470	+++	+++	++	+++	4.22	−6.01	0.59	0.28
3d	430	+++	+++	++	+++	3.63	−5.23	−1.44	0.26
3e	414	+++	+++	++	+++	2.68	−4.56	0.00	0.4
3f	404	+++	+++	++	+++	0.84	−2.95	0.05	0.5
4a	396	+++	+++	+++	+++	4.76	−6.33	−2.91	0.22
4b	456	+++	+++	+++	+++	4.55	−6.37	−2.22	0.22
4c	464	+++	+++	+++	+++	5.98	−7.8	−1.26	−0.16
4d	424	+++	+++	+++	+++	5.39	−7.02	−4.15	0.17
4e	408	+++	+++	+++	+++	5.00	−6.17	−2.06	0.23
4f	398	+++	+++	+++	+++	2.60	−4.74	−1.72	0.38
5a	394	+++	+++	+++	+++	4.25	−5.28	−2.91	0.28
5b	454	+++	+++	+++	+++	4.04	−5.32	−2.22	0.27
5c	462	+++	+++	+++	+++	5.47	−6.75	−1.26	0.20
5d	422	+++	+++	+++	+++	4.88	−5.97	−4.15	0.21
5e	406	+++	+++	+++	+++	4.49	−5.12	−2.06	0.29
5f	396	+++	+++	+++	+++	2.09	−3.69	−1.72	0.45
Neomycin	614	+++	+++	+++	+++	−10.03	0.06	2.61	0.58
Erythromycin	719	+++	+++	+++	+++	2.02	−3.49	11.29	0.47

+++, not toxic; ++, slightly toxic; −, highly toxic

MUT mutagenic, *TUMO* tumorigenic, *IRRI* irritant, *REP* reproductive effective, *CLP* cLogP, *S* solubility, *DL* drug likeness, *DS* drug-score

Table 3 Molinspiration calculations of compounds **3–5**

Compounds	Molinspiration calculations					Drug-likeness					
	TPSA	NONI	NV	nrotb	VOL	GPCRL	ICM	KI	NRL	PI	EI
3a	115	4	1	6	352	−0.25	−0.16	−0.37	−0.09	−0.22	0.07
3b	134	4	1	8	403	−0.26	−0.19	−0.36	−0.10	−0.24	0.03
3c	115	4	1	6	379	−0.24	−0.15	−0.36	−0.10	−0.25	0.04
3d	115	4	1	6	385	−0.27	−0.21	−0.38	−0.11	−0.26	0.02
3e	115	4	1	6	333	−0.37	−0.39	−0.43	−0.26	−0.33	−0.02
3f	141	4	0	6	343	−0.17	−0.06	−0.19	−0.06	−0.12	0.20
4a	93	2	1	4	341	0.06	0.16	0.05	0.25	−0.06	−0.01
4b	111	2	1	6	392	0.02	0.08	0.01	0.20	−0.10	−0.05
4c	93	2	1	4	368	0.06	0.14	0.03	0.22	−0.10	−0.04
4d	93	2	1	4	374	0.02	0.09	0.01	0.21	−0.11	−0.06
4e	93	2	1	4	322	−0.02	0.01	−0.01	0.05	−0.07	−0.12
4f	118	2	0	4	332	0.15	0.28	0.23	0.26	−0.06	0.12
5a	98	4	0	4	347	−0.01	−0.01	0.27	0.08	−0.16	−0.01
5b	116	4	0	6	398	−0.04	−0.06	0.21	0.05	−0.19	−0.04
5c	98	4	1	4	374	−0.01	−0.01	0.24	0.06	−0.19	−0.03
5d	98	4	1	4	380	−0.04	−0.07	0.22	0.05	−0.20	−0.05
5e	98	4	0	4	329	−0.12	−0.09	0.20	0.01	−0.27	−0.04
5f	124	4	0	4	339	0.05	0.07	0.42	0.07	−0.12	0.09
Neomycin	353	19	3	9	534	0.03	−0.22	−0.03	−0.13	0.55	0.47
Erythromycin	194	5	2	7	693	−0.42	−1.16	−1.14	−0.95	−0.08	−0.42

TPSA total polar surface area, *VOL* volume, *ONI* OH–NH interaction, *NV* number of violation, *GPCRL* GPCR ligand, *ICM* ion channel modulator, *KI* kinase inhibitor, *NRL* nuclear receptor ligand

water, diluted $NaHCO_3$ solution and again with cold water. The product was filtered off, dried, and recrystallized from alcohol. The completion of the reaction was monitored by TLC.

*4,6-Diacetylbenzene-1,3-diyl dibenzoate (**2a**)* Yield 74 %; mp 91 °C; FT-IR (KBr): 1755 (ester C=O), 1692 (C=O), 1601 (aromatic C=C), 1139 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 8.05 (d, 4H, $J_{2'-6'}$ & $J_{2''-6''}$ = 7.8 Hz), 7.01–8.51 (m, 8H, ArH), 2.57 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 158.1 (C-1 & C-3, C–O), 114.3 (C-2), 124.7 (C-4 & C-6), 128.9 (C-5), 165.9 (C of ester C=O), 130.5 (C-1′ & C-1″), 130.4 (C-2′, C-6′ & C-2″, C-6″), 128.9 (C-3′, C-5′ & C-3″, C-5″), 134.3 (C-4′ & C-4″), 199.5 (C of acetyl C=O), 29.6 (C of acetyl CH_3). Anal. Calcd. for $C_{24}H_{18}O_6$ (M^+): (402) C, 71.64; H, 4.51. Found: C, 71.69; H, 4.49.

*4,6-Diacetylbenzene-1,3-diyl bis(4-methoxybenzoate) (**2b**)* Yield 64 %; mp 95 °C; FT-IR (KBr): 1757 (ester C=O), 1696 (C=O), 1603 (aromatic C=C), 1143 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 8.09 (d, 4H, $J_{2'-6'}$ & $J_{2''-6''}$ = 7.9 Hz), 7.34–8.61 (m, 2H, ArH), 7.01 (d, 4H, $J_{3'-5'}$ & $J_{3''-5''}$ = 7.9 Hz), 3.71 (s, 6H, OCH_3), 2.51 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 157.9 (C-1 & C-3, C–O), 114.6 (C-2), 124.1 (C-4 & C-6), 128.4 (C-5), 165.4 (C of ester C=O), 122.8 (C-1′ & C-1″), 131.6 (C-2′, C-6′ & C-2″, C-6″), 115.2 (C-3′, C-5′ & C-3″, C-5″), 165.7 (C-4′ & C-4″, C–O), 56.1 (C of OCH_3), 199.9 (C of acetyl C=O), 29.4 (C of acetyl CH_3). Anal. Calcd. for $C_{26}H_{22}O_8$ (M^+): (462) C, 67. 53; H, 4.80. Found: C, 67.59; H, 4.78.

*4,6-Diacetylbenzene-1,3-diyl bis(4-chlorobenzoate) (**2c**)* Yield 63 %; mp 115 °C; FT-IR (KBr): 1761 (ester C=O), 1699 (C=O), 1606 (aromatic C=C), 1149 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 8.11 (d, 4H, $J_{2'-6'}$ & $J_{2''-6''}$ = 8.0 Hz), 7.41 (d, 4H, $J_{3'-5'}$ & $J_{3''-5''}$ = 8.0 Hz), 7.29–8.56 (m, 2H, ArH), 2.61 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 157.8 (C-1 & C-3, C–O), 114.5 (C-2), 124.3 (C-4 & C-6), 128.4 (C-5), 165.5 (C of ester C=O), 130.9 (C-1′ & C-1″), 130.7 (C-2′, C-6′ & C-2″, C-6″), 129.2 (C-3′, C-5′ & C-3″, C-5″), 139.9 (C-4′ & C-4″), 199.9 (C of acetyl C=O), 29.1 (C of acetyl CH_3). Anal. Calcd. for $C_{24}H_{16}Cl_2O_6$ (M^+): (470) C, 61.16; H, 3.42. Found: C, 61.22; H, 3.43.

*4,6-Diacetylbenzene-1,3-diyl bis(4-methylbenzoate) (**2d**)* Yield 69 %; mp 110 °C; FT-IR (KBr): 1751 (ester C=O), 1699 (C=O), 1609 (aromatic C=C), 1151 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 8.11 (d, 4H, $J_{2'-6'}$ & $J_{2''-6''}$ = 7.9 Hz), 7.44–8.65 (m, 2H, ArH), 7.18 (d, 4H, $J_{3'-5'}$ & $J_{3''-5''}$ = 7.9 Hz), 2.37 (s, 6H, CH_3 at C-4′ and C-4″ position in phenyl ring), 2.59 (s, 6H, CH_3 of acetyl group). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 158.5 (C-1 & C-3, C–O), 115.3 (C-2), 124.7 (C-4 & C-6), 128.9 (C-5), 164.9 (C of ester C=O), 122.4 (C-1′ & C-1″), 131.8 (C-2′, C-6′ & C-2″, C-6″), 115.7 (C-3′, C-5′ & C-3″, C-5″), 165.1 (C-4′ & C-4″, C–O), 25.6 (C of CH_3), 199.6 (C of acetyl C=O), 29.8 (C of acetyl CH_3). Anal. Calcd. for $C_{26}H_{22}O_6$ (M^+): (430) C, 72.55; H, 5.15. Found: C, 72.58; H, 5.18.

*4,6-Diacetylbenzene-1,3-diyl dithiophene-2-carboxylate (**2e**)* Yield 72 %; mp 105 °C; FT-IR (KBr): 1753 (ester C=O), 1689 (C=O), 1597 (aromatic C=C), 1131 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 7.09–8.58 (m, 8H, ArH), 2.64 (s, 6H, CH_3 of acetyl group). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 159.4 (C-1 & C-3, C–O), 114.9 (C-2), 125.4 (C-4 & C-6), 129.5 (C-5), 165.1 (C of ester C=O), 135.8 (C-1′ & C-1″), 135.9 (C-3′ & C-3″), 128.7 (C-4′ & C-4″), 133.8 (C-5′ & C-5″), 198.7 (C of acetyl C=O), 28.2 (C of acetyl CH_3). Anal. Calcd. for $C_{20}H_{14}O_6S_2$ (M^+): (414) C, 57.96; H, 3.40. Found: C, 57.99; H, 3.48.

*4,6-Diacetylbenzene-1,3-diyl dipyridine-3-carboxylate (**2f**)* Yield 74 %; mp 120 °C; FT-IR (KBr): 1749 (ester C=O), 1683 (C=O), 1599 (aromatic C=C), 1143 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 6.97–8.23 (m, 10H, ArH), 2.69 (s, 6H, CH_3 of acetyl group). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 160.7 (C-1 & C-3, C–O), 115.3 (C-2), 124.1 (C-4 & C-6), 128.8 (C-5), 163.9 (C of ester C=O), 135.4 (C-1′ & C-1″), 135.3 (C-2′ & C-2″), 127.2 (C-4′ & C-4″), 132.4 (C-5′ & C-5″), 135.1 (C-6′ & C-6″), 197.9 (C of acetyl C=O), 27.8 (C of acetyl CH_3). Anal. Calcd. for $C_{22}H_{16}O_6N_2$ (M^+): (404) C, 65.34; H, 3.99. Found: C, 65.38; H, 3.95.

*General procedure for the preparation of 1,1′-(4,6-dihydroxybenzene-1,3-diyl)bis(3-aryl/heteroarylpropane-1,3-dione) (**3a**–**3f**)*

1,3-Diaroyloxy/heteroaroyloxy-4,6-diacetylbenzene **2a**–**2f** (0.005 mol) was dissolved in 4 mL of DMSO. To that solution powdered NaOH (2 g) was added with vigorous stirring for about 5 min. The stirring was continued for 5 min further. The reaction mixture was then cooled and poured on cold water. The pale yellow solid product obtained was washed with water, dried, and recrystallized from alcohol.

*1,1′-(4,6-Dihydroxybenzene-1,3-diyl)bis(3-phenylpropane-1,3-dione) (**3a**)* Yield 74 %; mp 121 °C; FT-IR (KBr): 3425 (OH), 1740 (C=O), 1601 (aromatic C=C), 1139 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 15.89 (s, 2H, enolic OH), 12.01 (s, 2H, 4-OH, 6-OH), 8.43 (s, 2H,–CH=), 7.48 (d, 4H, $J_{2'-6'}$ & $J_{2''-6''}$ = 8.4 Hz), 6.59–7.89 (m, 8H, ArH). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 189.1 (C-1 &

C-3), 133.3 (C-2), 170.6 (C-4 & C-6), 105.8 (C-5), 190.4 (C of C=O), 185.5 (C of enolic C–O), 93.5 (C of –C=H), 130.4 (C-1′ & C-1″), 127.1 (C-2′, C-6′ & C-2″, C-6″), 128.9 (C-3′, C-5′ & C-3″, C-5″), 129.3 (C-4′ & C-4″). Anal. Calcd. for $C_{24}H_{18}O_6$ (M^+): (402) C, 71.64; H, 4.51. Found: C, 71.66; H, 4.54.

*1,1′-(4,6-Dihydroxybenzene-1,3-diyl)bis[3-(4-methoxyphenyl) propane-1,3-dione] (**3b**)* Yield 64 %; mp 155 °C; FT-IR (KBr): 3429 (OH), 1747 (C=O), 1604 (aromatic C=C), 1146 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 15.91 (s, 2H, enolic OH), 12.08 (s, 2H, 4-OH, 6-OH), 8.39 (s, 2H,–CH=), 7.59 (δ, 4H, $J_{2'-6'}$ & $J_{2''-6''}$ = 8.1 Hz), 7.16 (d, 4H, $J_{3'-5'}$ & $J_{3''-5''}$ = 8.1 Hz), 7.31–8.59 (m, 2H, ArH), 3.81 (s, 6H, OCH_3). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 189.8 (C-1 & C-3), 134.1 (C-2), 169.5 (C-4 & C-6), 104.5 (C-5), 189.6 (C of C=O), 184.6 (C of enolic C–O), 94.2 (C of –C=H), 131.2 (C-1′ & C-1″), 128.7 (C-2′, C-6′ & C-2″, C-6″), 128.6 (C-3′, C-5′ & C-3″, C-5″), 160.2 (C-4′ & C-4″), 55.9 (C of CH_3). Anal. Calcd. for $C_{26}H_{22}O_8$ (M^+): (462) C, 67.53; H, 4.80. Found: C, 67.56; H, 4.81.

*1,1′-(4,6-Dihydroxybenzene-1,3-diyl)bis[3-(4-chlorophenyl) propane-1,3-dione] (**3c**)* Yield 69 %; mp 135 °C; FT-IR (KBr): 3434 (OH), 1740 (C=O), 1602 (aromatic C=C), 1141 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 15.99 (s, 2H, enolic OH), 12.11 (s, 2H, 4-OH, 6-OH), 8.31 (s, 2H,–CH=), 8.13 (d, 4H, $J_{2'-6'}$ & $J_{2''-6''}$ = 8.0 Hz), 7.49 (d, 4H, $J_{3'-5'}$ & $J_{3''-5''}$ = 8.0 Hz), 7.48–8.31 (m, 2H, ArH). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 190.2 (C-1 & C-3), 134.5 (C-2), 169.8 (C-4 & C-6), 105.9 (C-5), 190.4 (C of C=O), 186.3 (C of enolic C–O), 95.4 (C of –C=H), 132.4 (C-1′ & C-1″), 129.4 (C-2′, C-6′ & C-2″, C-6″), 128.9 (C-3′, C-5′ & C-3″, C-5″), 134.2 (C-4′ & C-4″). Anal. Calcd. for $C_{24}H_{16}Cl_2O_6$ (M^+): (470) C, 61.16; H, 3.42. Found: C, 61.20; H, 3.45.

*General procedure for the preparation of 4,6-bis(5-aryl/heteroaryl-1,2-oxazol-3-yl)benzene-1,3-diol (**4a**–**4f**)*

The mixture of 1,1′-(4,6-dihydroxybenzene-1,3-diyl)bis (3-aryl/heteroarylpropane-1,3-dione) **3a**–**3f** (0.1 mol), hydroxylamine hydrochloride (0.004 mol), KOH (1 g), and ethanol (30 mL) was refluxed for 5 h. It was cooled to room temperature and poured onto ice cold water and acidified with diluted HCl. A solid slowly separated out, it was crystallized from ethanol.

*4,6-Bis(5-phenyl-1,2-oxazol-3-yl)benzene-1,3-diol (**4a**)* Yield 75 %; mp 165 °C; FT-IR (KBr): 3401 (OH), 1712 (C=N), 1608 (aromatic C=C), 1154 (C–O). ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 6.32–8.49 (m, 14H, ArH), 5.23 (s, 2H, OH). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 157.4 (C-1 & C-3, C–O), 104.9 (C-2), 114.5 (C-4 & C-6), 129.4 (C-5), 162.6 (C of C=N, oxazole), 98.8 (C of –C=H), 170.6 (C of C–O, oxazole), 131.6 (C-1′ & C-1″), 128.7 (C-2′, C-6′ & C-2″, C-6″), 130.3 (C-3′, C-5′ & C-3″, C-5″), 129.4 (C-4′ & C-4″). Anal. Calcd. for $C_{24}H_{16}N_2O_4$ (M^+): (396) C, 72.72; H, 4.07. Found: C, 72.69; H, 4.13.

*4,6-Bis[5-(4-methoxyphenyl)-1,2-oxazol-3-yl]benzene-1,3-diol (**4b**)* Yield 65 %; mp 175 °C; FT-IR (KBr): 3412 (OH), 1714 (C=N), 1603 (aromatic C=C), 1159 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 5.32 (s, 2H, OH), 6.39–8.41 (m, 12H, ArH), 3.76 (s, 6H, OCH_3). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 158.2 (C-1 & C-3, C–O), 105.2 (C-2), 115.3 (C-4 & C-6), 130.3 (C-5), 161.8 (C of C=N, oxazole), 98.9 (C of –C=H), 170.5 (C of C–O, oxazole), 131.8 (C-1′ & C-1″), 128.7 (C-2′, C-6′ & C-2″, C-6″), 115.3 (C-3′, C-5′ & C-3″, C-5″), 161.4 (C-4′ & C-4″), 56.9 (C of OCH_3). Anal. Calcd. for $C_{26}H_{20}N_2O_6$ (M^+): (456) C, 68.42; H, 4.42. Found: C, 68.49; H, 4.44.

*4,6-Bis[5-(4-chlorophenyl)-1,2-oxazol-3-yl]benzene-1,3-diol (**4c**)* Yield 64 %; mp 180 °C; FT-IR (KBr): 3415 (OH), 1707 (C=N), 1601 (aromatic C=C), 1161 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 5.29 (s, 2H, OH), 6.43–8.59 (m, 12H, ArH). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 158.6 (C-1 & C-3, C–O), 105.3 (C-2), 115.7 (C-4 & C-6), 130.2 (C-5), 161.8 (C of C=N, oxazole), 99.9 (C of –C=H), 171.5 (C of C–O, oxazole), 132.7 (C-1′ & C-1″), 129.8 (C-2′, C-6′ & C-2″, C-6″), 131.2 (C-3′, C-5′ & C-3″, C-5″), 135.6 (C-4′ & C-4″). Anal. Calcd. for $C_{24}H_{14}Cl_2N_2O_4$ (M^+): (465) C, 61.95; H, 3.03. Found: C, 61.98; H, 3.08.

*4,6-Bis[5-(4-methylphenyl)-1,2-oxazol-3-yl]benzene-1,3-diol (**4d**)* Yield 71 %; mp 150 °C; FT-IR (KBr): 3419 (OH), 1712 (C=N), 1599 (aromatic C=C), 1157 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 5.21 (s, 2H, OH), 6.41–8.51 (m, 12H, ArH), 2.39 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 159.2 (C-1 & C-3, C–O), 105.8 (C-2), 115.9 (C-4 & C-6), 131.6 (C-5), 162.6 (C of C=N, oxazole), 100.2 (C of –C=H), 169.5 (C of C–O, oxazole), 132.1 (C-1′ & C-1″), 129.6 (C-2′, C-6′ & C-2″, C-6″), 128.3 (C-3′, C-5′ & C-3″, C-5″), 139.8 (C-4′ & C-4″), 25.3 (C of CH_3). Anal. Calcd. for $C_{26}H_{20}N_2O_4$ (M^+): (424) C, 73.57; H, 4.75. Found: C, 73.60; H, 4.74.

*4,6-Bis[5-(thiophen-2-yl)-1,2-oxazol-3-yl]benzene-1,3-diol (**4e**)* Yield 73 %; mp 169 °C; FT-IR (KBr): 3423 (OH), 1602 (aromatic C=C), 1153 (C–O), 1716 (C=N); ^{1}H NMR (DMSO-d_6, d, 400 MHz) 5.25 (s, 2H, OH), 6.53–8.69

(m, 10H, ArH); ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 158.2 (C-1 & C-3, C–O), 105.2 (C-2), 115.3 (C-4 & C-6), 130.3 (C-5), 161.8 (C of C=N, oxazole), 98.9 (C of –C=H), 170.5 (C of C–O, oxazole), 134.8 (C-1′ & C-1″), 136.9 (C-3′ & C-3″), 129.4 (C-4′ & C-4″), 134.3 (C-5′ & C-5″). Anal. Calcd. for $C_{20}H_{12}N_2O_4S_2$ (M^+): (408) C, 58.81; H, 2.96. Found: C, 58.84; H, 2.99.

4,6-Bis[5-(pyridin-3-yl)-1,2-oxazol-3-yl]benzene-1,3-diol ***(4f)*** Yield 75 %; mp 170 °C; FT-IR (KBr): 3429 (OH), 1718 (C=N), 1606 (aromatic C=C), 1157 (C–O); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 6.49–8.63 (m, 12H, ArH), 5.30 (s, 2H, OH). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 155.8 (C-1 & C-3, C–O), 105.8 (C-2), 115.8 (C-4 & C-6), 131.7 (C-5), 162.5 (C of C=N, oxazole), 99.8 (C of –C=H), 171.2 (C of C–O, oxazole), 135.4 (C-1′ & C-1″), 150.6 (C-2′ & C-2″), 149.2 (C-4′ & C-4″), 125.4 (C-5′ & C-5″), 135.9 (C-6 & C-6″). Anal. Calcd. for $C_{22}H_{14}N_4O_4$ (M^+): (398) C, 66.33; H, 3.54. Found: C, 66.35; H, 3.56.

*General procedure for the preparation of 4,6-bis(5-aryl/heteroaryl-1H-pyrazol-3-yl)benzene-1,3-diol (**5a–5f**)*

The mixture of 1,1′-(4,6-dihydroxybenzene-1,3-diyl)bis(3-aryl/heteroarylpropane-1,3-dione) **3a–3f** (0.1 mol), hydrazine hydrate (0.004 mol), KOH (1 g), and ethanol (30 mL) was refluxed for 5 h. It was cooled to room temperature and poured onto ice cold water and acidified with diluted HCl. A solid slowly separated out, it was crystallized from ethanol.

4,6-Bis(5-phenyl-1H-pyrazol-3-yl)benzene-1,3-diol ***(5a)*** Yield 76 %; mp 195 °C; FT-IR (KBr): 3419 (OH), 1718 (C=N), 1611 (aromatic C=C); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 6.47–8.39 (m, 14H, ArH), 5.46 (s, 2H, OH). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 158.9 (C-1 & C-3, C–O), 105.3 (C-2), 115.3 (C-4 & C-6), 128.7 (C-5), 148.9 (C of C=N, pyrazole), 100.1 (C of –C=H), 150.9 (C of C–N, pyrazole), 134.2 (C-1′ & C-1″), 129.2 (C-2′, C-6′ & C-2″, C-6″), 131.1 (C-3′, C-5′ & C-3″, C-5″), 129.2 (C-4′ & C-4″). Anal. Calcd. for $C_{24}H_{18}N_4O_2$ (M^+): (394) C, 73.08; H, 4.60. Found: C, 73.10; H, 4.61.

4,6-Bis[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]benzene-1,3-diol ***(5b)*** Yield 68 %; mp 180 °C; FT-IR (KBr): 3415 (OH), 1718 (C=N), 1609 (aromatic C=C); ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 6.49–8.53 (m, 12H, ArH), 5.38 (s, 2H, OH), 3.69 (s, 6H, OCH_3). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 157.5 (C-1 & C-3, C–O), 105.1 (C-2), 115.4 (C-4 & C-6), 129.2 (C-5), 149.3 (C of C=N, pyrazole), 99.5 (C of –C=H), 149.8 (C of C–N, pyrazole), 126.2 (C-1′ & C-1″), 128.7 (C-2′, C-6′ & C-2″, C-6″), 115.5 (C-3′, C-5′ & C-3″, C-5″), 161.3 (C-4′ & C-4″), 57.1 (C of OCH_3). Anal. Calcd. for $C_{26}H_{22}N_4O_4$ (M^+): (454) C, 68.71; H, 4.88. Found: C, 68.69; H, 4.89.

4,6-Bis[5-(4-chlorophenyl)-1H-pyrazol-3-yl]benzene-1,3-diol ***(5c)*** Yield 64 %; mp 185 °C; FT-IR (KBr): 3417 (OH), 1713 (C=N), 1606 (aromatic C=C); ^{1}H NMR (DMSO-d_6, d, 400 MHz) 6.41–8.56 (m, 12H, ArH), 5.34 (s, 2H, OH). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 158.2 (C-1 & C-3, C–O), 105.9 (C-2), 114.8 (C-4 & C-6), 128.8 (C-5), 148.9 (C of C=N, pyrazole), 99.3 (C of –C=H), 148.5 (C of C–N, pyrazole), 132.4 (C-1′ & C-1″), 128.3 (C-2′, C-6′ & C-2″, C-6″), 129.3 (C-3′, C-5′ & C-3″, C-5″), 135.6 (C-4′ & C-4″). Anal. Calcd. for $C_{24}H_{16}Cl_2N_4O_2$ (M^+): (463) C, 62.22; H, 3.48. Found: C, 62.25; H, 3.45.

4,6-Bis[5-(4-methylphenyl)-1H-pyrazol-3-yl]benzene-1,3-diol ***(5d)*** Yield 70 %; mp 190 °C; FT-IR (KBr): 3421 (OH), 1719 (C=N), 1604 (aromatic C=C). ^{1}H NMR (DMSO-d_6, d, 400 MHz) 5.31 (s, 2H, OH), 6.44–8.56 (m, 12H, ArH), 2.36 (s, 6H, CH_3). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 158.7 (C-1 & C-3, C–O), 106.4 (C-2), 115.9 (C-4 & C-6), 130.3 (C-5), 149.3 (C of C=N, pyrazole), 98.7 (C of –C=H), 150.6 (C of C–N, pyrazole), 127.4 (C-1′ & C-1″), 129.7 (C-2′, C-6′ & C-2″, C-6″), 128.5 (C-3′, C-5′ & C-3″, C-5″), 139.7 (C-4′ & C-4″), 25.7 (C of CH_3). Anal. Calcd. for $C_{26}H_{22}N_4O_2$ (M^+): (422) C, 73.92; H, 5.25. Found: C, 73.90; H, 5.21.

4,6-Bis[5-(thiophen-2-yl)-1H-pyrazol-3-yl]benzene-1,3-diol ***(5e)*** Yield 73 %; mp 180 °C; FT-IR (KBr): 3425 (OH), 1721 (C=N), 1600 (aromatic C=C). ^{1}H NMR (DMSO-d_6, δ, 400 MHz) 6.66–8.59 (m, 10H, ArH), 5.39 (s, 2H, OH); ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 159.2 (C-1 & C-3, C–O), 105.8 (C-2), 115.6 (C-4 & C-6), 131.4 (C-5), 150.4 (C of C=N, pyrazole), 100.9 (C of –C=H), 137.6 (C of C–N, pyrazole), 140.8 (C-1′ & C-1″), 126.9 (C-3′ & C-3″), 128.1 (C-4′ & C-4″), 127.1 (C-5′ & C-5″). Anal. Calcd. for $C_{20}H_{14}N_4O_2S_2$ (M^+): (406) C, 59.10; H, 3.47. Found: C, 59.16; H, 3.51.

4,6-Bis[5-(pyridin-3-yl)-1H-pyrazol-3-yl]benzene-1,3-diol ***(5f)*** Yield 75 %; mp 175 °C; FT-IR (KBr): 3435 (OH), 1721 (C=N), 1604 (aromatic C=C); ^{1}H NMR (DMSO-d_6, d, 400 MHz) 5.33 (s, 2H, OH), 6.68–8.73 (m, 12H, ArH). ^{13}C NMR (DMSO-d_6, δ, 400 MHz) 157.6 (C-1 & C-3, C–O), 105.3 (C-2), 114.5 (C-4 & C-6), 129.3 (C-5), 148.7 (C of C=N, pyrazole), 99.2 (C of –C=H), 149.6 (C of C–N, pyrazole), 134.6 (C-1′ & C-1″), 149.5 (C-2′ & C-2″), 148.5 (C-4′ & C-4″), 125.3 (C-5′ & C-5″), 136.4 (C-6 & C-6″). Anal. Calcd. for $C_{22}H_{16}N_6O_2$ (M^+): (396) C, 66.66; H, 4.07. Found: C, 66.69; H, 4.10.

In vitro antimicrobial screening

All the operations were carried out under aseptic conditions. The well diffusion method was employed in the antibacterial screening procedure with methanol extract of synthesized compounds **3a–3f**, **4a–4f**, and **5a–5f**. The cultures of bacterial strains were inoculated in 10 mL nutrient agar medium and was sterilized by autoclaving. To this sterilized nutrient medium, 1 mL of 1-day-old bacterial culture was added and stirred well; this medium was poured into Petri dishes. The well impregnated with 100 μg mL^{-1} of the newly synthesized compounds were introduced aseptically in the nutrient agar plate. The neomycin and erythromycin were used as a control. All the nutrient agar plates were incubated at 37 °C for 24 h after which the plates were observed for clear zone of inhibition. The results are listed in Table 1.

Minimum inhibitory concentration (MIC, mg mL^{-1})

The MICs of the chemical compounds assays were carried out as described by Clause (1989). The MICs of the chemical compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no growth (i.e., no turbidity) of inoculated bacteria.

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