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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

QSAR modeling of synthesized 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones as potent antibacterial agents

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Abstract Present communication elicits the designing and synthesis of 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones as potential antibacterial agents. A number of substituted 2-amino benzothiazoles, 2-amino-5-[(*E*)-phenyl diazenyl] benzoic acid, and 2-phenyl-4*H* benzo[d] [1,3] oxazin-4-one were synthesized as the precursor substrates. The compounds were synthesized in excellent yields and the structures were corroborated on the basis of IR, ^{1}H NMR, Mass, and elemental analysis data. These compounds were screened in vitro for their antibacterial activity against a representative panel of Gram positive and Gram negative bacteria and models were generated through quantitative structure–activity relationship (QSAR).The activity contributions due to structural and substituent effects were determined using sequential regression procedure. The antimicrobial assay data show that the synthesized compounds are found to manifest profound antimicrobial activity.

Keywords Quinazoline-4(3*H*)-ones · Benzothiazole · Quantitative structure–activity relationship · Antibacterial activity

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Introduction

Quinazoline-4(3*H*)-one ring system has been consistently regarded as a promising privileged structural icon owing to its pharmacodynamic versatility in many of its synthetic derivatives as well as in several naturally occurring alkaloids isolated from animals, families of plant kingdoms, and micro-organisms (Witt and Bergman, 2003; Wong and Ganesan, 2000; Micheal, 2001). A systematic perusal of literature reveals that quinazoline derivatives encompass a broad spectrum of pharmaceutical activity profile viz, antitumor, sedative, analgesic, antidiabetic, antibacterial, antifungal, and antiinflammatory (Dandia and Singh, 2005; Grover and Kini, 2006; Reddy *et al*., 2003; Kumar *et al*., 2005; Bertelli *et al*., 2000; Malecki *et al*., 2004). The quinazoline nucleus is the scaffold of many antitumor drugs mainly acting as inhibitors of tyrosine kinase receptors (TKR). Over expression of these receptors has been observed in a number of cancers (e.g., breast, ovarian, colon, and prostate). Quinazoline derivatives have a therapeutic potential as an antiinvasive agents with potential activity in early and advanced solid tumors, metastatic bone disease and leukemia (Ashcroft *et al*., 2003). Some of the known quinazoline derivatives are reported to exhibit remarkable anticancer activity. More specifically trimetrexate (TMQ) and piritrexim (PTX) have been considered as new generation potent lipophilic DHFR inhibitors (Sielecki *et al*., 2001). In particular, quinazoline-4-one alkaloids such as asperlicin C, possessing cholecystokinin antagonist properties, and benzomalvins, which are neurokinin receptor antagonists, as well as other similar molecules has gained significant importance. These alkaloids are often biosynthetically derived from anthranilic acid and chiral amino acids, and as a result contain a chiral center in the R-position of the 2-substituent. Thus, in view of the broad horizon of

pharmacological potential associated with 2,3-disubstituted 3*H*-quinazoline-4-ones, it has been realized that this heterocyclic architecture represents one of the most indispensable groups of heterocycles. A number of such derivatives corroborates as the important constituents in the drug design studies vis a vis to synthesize certain drug compounds.

Likewise, benzothiazole is also one of the most potent heterocyclic scaffold possessing a wide range of applications in bio-organic and medicinal chemistry armamentarium. Moreover, 2-aminobenzothiazoles governs a plethora of applications in drug discovery and development for the treatment of diabetes (Suter and Zutter, 1967), epilepsy (Hays *et al*., 1994; Jimonet *et al*., 1999; He *et al*., 2002), inflammation (Sawhney *et al*., 1978), amyotrophic lateral sclerosis (Bensimon *et al*., 1994), analgesia (Foscolos *et al*., 1977), tuberculosis (Shirke *et al*., 1990), and viral infections (Paget *et al*., 1969).

Hence, buoyed from these findings and in view of the significant biological potential alluded by these heterocycles, it was thought worthwhile to synthesize their amalgamated product and to explore their antibacterial potential. Considering this rationale we have designed and synthesized a new series of quinazolin-4(3*H*) ones fused with benzothiazoles followed by their screening as potential antibacterial agents. We have reported herein the reaction of substituted 2-amino benzothiazole with 2-amino-5-[(*E*)-phenyl diazenyl] benzoyl chloride (Route A) and 2-phenyl-4*H* benzo[d] [1,3] oxazin-4-one (Route B) in order to obtain 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-one as the target compounds.

Chemistry

In view of the high biological activity profile of quinazoline compounds, we have developed a new and more efficient synthesis of this class of compounds. The classical synthetic approach to quinazolines viz; the Niementowski quinazoline reaction involves the formation of the intermediate 3(*H*)-4-quinazolinone (derived from anthranilic acid) followed by the formation of 4-chloroquinazoline and subsequent nucleophilic aromatic substitution at the pyrimidine ring (Orfi *et al*., 2004). Keeping this in view, we have developed a modified strategy to prepare some new 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones considering two different reaction routes. Route A delineates the reaction of substituted benzothiazoles with 2-amino-5-[(*E*)-phenyl diazenyl] benzoyl chloride whereas Route B undertakes the reaction of substituted benzothiazoles with 2-phenyl-4*H* benzo[d] [1,3] oxazin-4-one (prepared from ethyl anthranilate and benzoic anhydride).

In order to obtain the substituted 2-aminobenzothiazoles (**4**) as the precursor substrates, aryl thioureas (**2**) were prepared by condensing together pertinent aniline derivatives and ammonium thiocyanate. Furthermore, as per the reaction conditions of Hugerschoff's synthesis the construction of the benzothiazole system involves oxidative cyclization of arylthioureas with bromine. It is known for the Hugerschoff reaction that excess bromine usually produces the perbromide (as the byproduct) of the aminobenzothiazole, which can then brominate the benzene ring under prolonged reaction conditions. Therefore, as an alternative approach, to accomplish the synthesis of 2-aminobenzothiazole in a facile way, the reaction was conducted with 1 molar equivalent of liquid bromine in chloroform at room temperature to provide a series of substituted 2-amino benzothiazoles (**4**) in 60–75% yields.

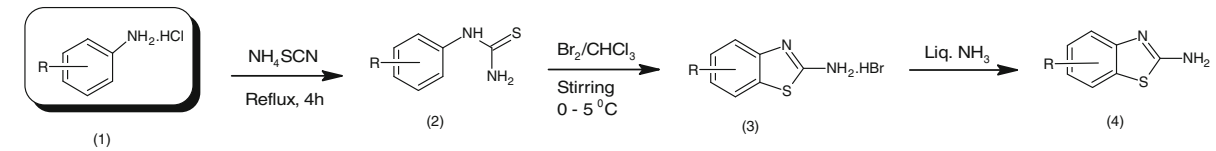
As per the synthetic strategy depicted for route A, anthranilic acid reacts with diazonium salt to form 2-amino-5-[(*E*)-phenyl diazenyl] benzoic acid (**5**),which in turn gives 2-amino-5-[(*E*)-phenyl diazenyl] benzoyl chloride(**6**) by treating with PCl_5. Compound (**6**) reacts with substituted 2-amino benzothiazole to form compound (**7**) which was further benzoylated to yield 8. Enolization of Compound (**8**) gives compound **9** and its subsequent cyclization ultimately yielded the product 10, after eliminating a water molecule. Furthermore, treatment of compound (**10**) with sodium dithionite provided compound (**11**) after reduction of the aryl azo moiety and upon deamination, compound (**12**) has been obtained.

In an alternate manner, according to the route B, esterification of anthranilic acid (**13**) was carried out to obtain ethyl anthranilate (**14**). Compound (**14**) reacts with benzoic anhydride to form the cyclic product **2**-phenyl-4*H* benzo[d] [1,3] oxazin-4-one (**15**) as the desired target. An overview of synthetic routes is depicted in Scheme 1.

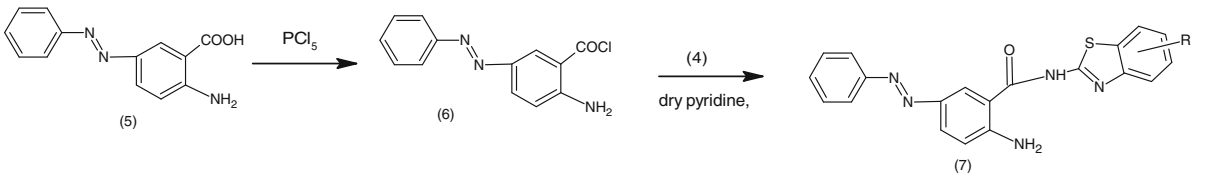
Antibacterial activity and QSAR

The wide range of activity profile of quinazolin-4(3*H*)-ones prompted us to develop efficacious insight for its antibacterial activity. All the synthesized compounds were screened for their in vitro antibacterial activity against Gram positive (*B. subtilis* and *S. aureus*) and Gram negative (*E. coli* and *K. pneumoniae*) bacteria. It was considered of interest to investigate the influence of substituents on the anticipated biological activity. All the synthesized compounds showed a remarkable effect on the bacteriocidal/bacteriostatic potency of the synthesized quinazolin-4(3*H*)-ones as has been revealed from the data presented in Table 1.

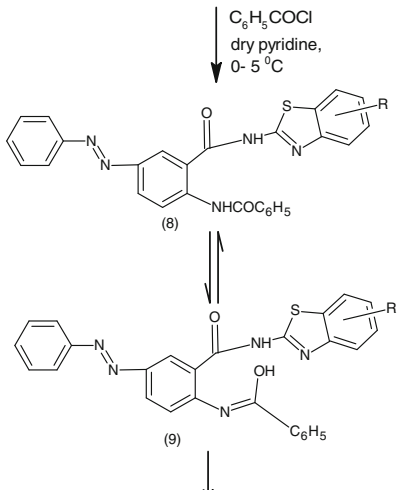
Quantitative structure–activity relationship (QSAR) models correlate molecular chemical structure to biological activity. Appropriate changes in the chemical structure altering the electron distribution within a molecule, are directly responsible for the activity of the molecule



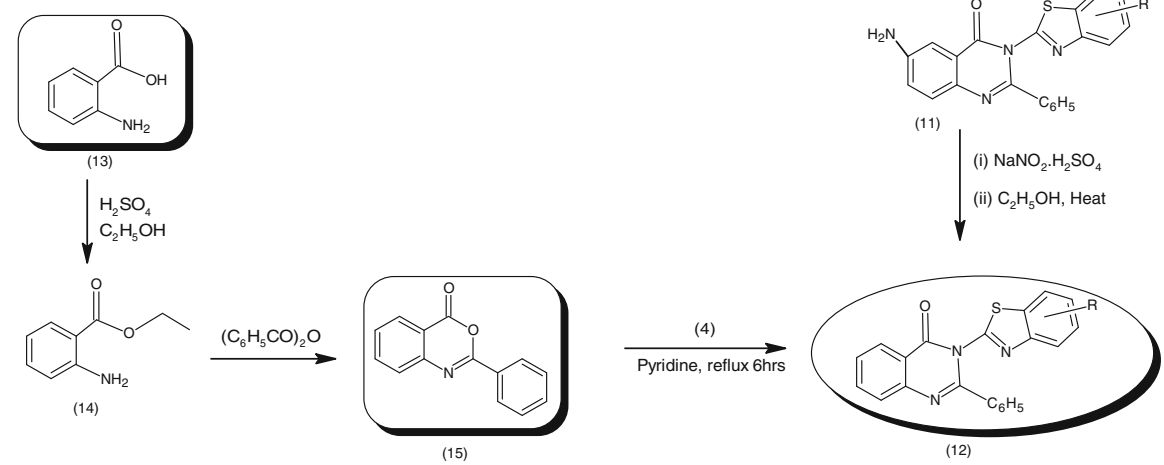
Route A



Entry	R
12a	H
12b	5-Cl
12c	5-OH
12d	6-OH
12e	6-Br
12f	5-Br
12g	5-CH_3
12h	6-CH_3
12i	4-OH
12j	7-OH
12k	5-OCH_3
12l	4-OCH_3
12m	4-CH_3
12n	7-CH_3
12o	4-Br
12p	7-Br



Route B



Scheme 1 Overview of synthetic strategy for the synthesis of 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones (**12a**–**p**)

Table 1 In vitro antimicrobial activities tested against Gram positive and Gram negative bacteria

Entry	R	*B. subtilis* pIC_{50}	*S. aureus* pIC_{50}	*E. coli* pIC_{50}	*K. pneumoniae* pIC_{50}
12a	–H	−2.528	−2.602	−2.638	−2.643
12b	5-Cl	−1.602	−1.398	−1.699	−1.778
12c	5-OH	−3.116	−3.146	−3.161	−3.193
12d	6-OH	−2.905	−2.908	−2.982	−3.052
12e	6-Br	−1.204	−1.301	−1.311	−1.342
12f	5-Br	−1.342	−0.301	−0.477	−0.602
12g	5-CH_3	−1.740	−1.845	−2.301	−2.114
12h	6-CH_3	−1.431	−1.699	−2.041	−2.097
12i	4-OH	−2.846	−2.903	−3.053	−3.057
12j	7-OH	−2.446	−2.778	−2.869	−2.908
12k	5-OCH_3	−2.358	−2.531	−2.785	−2.839
12l	4-OCH_3	−2.215	−2.477	−2.677	−2.719
12m	4-CH_3	−2.009	−1.903	−2.146	−2.100
12n	7-CH_3	−2.301	−2.380	−2.398	−2.380
12o	4-Br	−1.000	−1.079	−1.079	−1.146
12p	7-Br	−0.301	−0.845	−1.255	−1.415

(Hansch and Fujita, 1964; Free and Wilson, 1964; Kubinyi, 1993). This fundamental ideology can be used to elucidate a quantitative description of changes in biological activity arising due to the presence of the functional groups within a molecule. QSAR modeling requires three main features: a data set of molecules, appropriate descriptors and an efficient statistical method for capturing correlation. Descriptors are characteristic properties of molecules, often represented as numerical values, which facilitate the analysis of chemical structure. A wide variety of molecular descriptors are available and descriptor selection is an integral process in QSAR modeling (Sharma *et al*., 2004).

QSAR methodology, developed by Hansch (Sharma *et al*., 2009) provided a foundation to establish a correlation between physicochemical properties and elicited biological activity using multivariable regression. Regression analysis models the activities of molecules through an equation constructed using a linear combination of physicochemical properties. The coefficient for each variable in the equation can, consequently, be examined to determine the extent to which each property contributes towards the activity of the molecule.

Prompted by these findings, the QSAR analysis of synthesized quinazoline-4(3*H*)-one series has been performed based on the assumption of linear additive contributions of the different physicochemical properties. In order to deduce the correlation of observed activity, in terms of pIC_{50} of reported compounds with different structural parameters, a systematic QSAR investigation has been carried out using the model proposed by Hansch and coworkers. The activity data, pIC_{50} represents the concentration of compounds that inhibited visible growth. The same are further expressed as pIC_{50} on molar basis and used as dependent variables to get linear relationship in QSAR model. The calculated parameters used in the present study include log of octanol–water partition coefficient (LOG P), molar refractivity (MR) and Connolly accessible area (CAA), Connolly molecular area (CMA), dipole–dipole energy (DDE), Van der Waals volume (VDW) and non-Van der Waals volume (NVDW). The above-mentioned parameters were calculated by using

Table 2 Values of selected descriptors calculated for 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones (**12a–p**)

Compd[a]	HOMO	LUMO	CAA	CMA	CSEV	LOG P	DDE	MR	VDW	NVDW
–H	−9.0261	−0.6171	576.858	313.905	272.093	5.9682	−6.4505	102.307	12.8305	−5.9131
5-Cl	−9.0952	−0.7946	600.026	328.387	286.135	6.5264	−5.4122	107.111	13.4327	−6.0882
5-OH	−8.7861	−0.6936	584.507	318.877	276.378	5.5787	−6.3366	104.001	11.5711	−6.3986
6-OH	−8.9855	−0.609	584.872	318.894	276.219	5.5787	−6.277	104.001	11.6351	−6.3874
6-Br	−9.2298	−0.8948	608.137	333.543	291.829	6.7971	−5.3819	109.929	13.9503	−6.1557
5-Br	−9.1714	−0.8368	608.213	333.592	291.817	6.7971	−5.4688	109.929	13.8909	−6.1545
5-CH_3	−8.909	−0.591	607.41	332.46	288.63	6.4533	−6.668	107.348	13.585	−6.126
6-CH_3	−8.991	−0.6044	607.298	332.479	288.683	6.4533	−6.6811	107.348	13.584	−6.1145
4-OH	−8.7776	−0.6169	582.948	318.974	276.789	5.5787	−5.9735	104.001	19.8508	−6.5624
7-OH	−8.7179	−0.6577	583.537	318.519	276.441	5.5787	−5.4508	104.001	11.6381	−6.488
5-OCH_3	−8.7458	−0.6438	620.972	339.965	294.733	5.8418	−6.3259	108.77	15.5769	−2.4225
4-OCH_3	−8.7209	−0.576	619.316	340.054	295.137	5.8418	−5.7843	108.77	19.5692	−2.7914
4-CH_3	−8.895	−0.601	596.47	332.7	291.69	6.4533	−6.921	107.348	13.571	−6.45
7-CH_3	−8.7468	−0.8009	598.56	329.491	288.84	6.4533	−8.1377	107.348	13.584	−4.86
4-Br	−9.1257	−0.8476	600.123	333.481	294.487	6.7971	−4.3452	109.929	13.7398	−6.5328
7-Br	−9.1452	−0.8139	604.514	332.345	291.958	6.7971	−3.4214	109.929	14.128	−6.247

[a] Substituent numbering is done as per their location in 2-amino benzothiazole nucleus

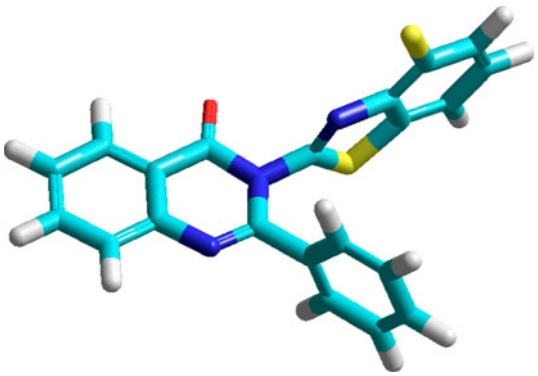


Fig. 1 PM3 optimized geometry of more active 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones

Chem3D 6.0 software as depicted in Table 2. Further, HOMO and LUMO energies were calculated by semi empirical PM3 (Stewart, 1989) method using MOPAC 6.0 package (Stewart, 1990) implemented in Chem3D 6.0 package. PM3 optimized geometry of more active 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones is shown in Fig. 1.

Correlation studies were performed for various descriptors, and intercorrelated parameters were discarded depending upon their individual correlation with biological activities as indicated in Table 3. The best fit between pIC_{50} values and these explaining parameters were obtained through multiple regression analysis (MRA) employing the method of least square using Valstat (Valstat). The most commonly used statistical method, multiple linear regression (MLR) analysis, was applied to create QSAR models and to obtain statistical data values, i.e., correlation coefficient (r), standard deviation (s), F test, cross-validated correlation coefficient (q^2), and sum of square standard error (S_{PRESS}). These statistical data were used to evaluate the obtained QSAR models. The best-derived QSAR model was used to predict activity of the untested compounds and to suggest structural feature(s) which should be modified in order to improve activity. The predictive powers of the equations were validated by the leave one out (LOO) cross validation method. In the equations described below, n is the number of data points and r is the correlation coefficient. %EV, F, SEE, PRESS, SSY, r^2_{cv}, r^2_{bsp}, S_{PRESS} are percentage of explained variance, ratio between the variances of observed and calculated activities, standard error of estimate, predicted residual sum of squares, total sum of squares, cross-validated R^2, Bootstrapping r^2, and standard deviation error of prediction, respectively (Sharma *et al*., 2005).

QSAR equations for antibacterial profile against *B. subtilis*

$$pIC_{50} = [-8.462(\pm 2.605)] + LOGP[1.311(\pm 0.332)] + DDE[0.273(\pm 0.166)] \quad (1)$$

Contribution of parameters to model is LOGP:DDE::5.08325:1

$n = 12$, $r = 0.972$, $r^2 = 0.944$, variance = 0.051, $S = 0.225$, $F = 76.35$, PRESS = 0.457, SSY = 8.21, PRESS/SSY = 0.056, $r^2_{cv} = 0.944$, % EV = 93.878, SEE = 0.195, Bootstrapping $r^2 = 0.944$, Bootstrapping $S = 0.031$, $Q^2 = 0.887$, $S_{PRESS} = 0.320$, SDEP = 0.277.

Equation 1 explains up to 93.88% of the variation of the activities. From the Eq. 1 of the proposed QSAR model it is revealed that the LOG P and DDE are the main governing factors to control the observed activities of

Table 3 Correlation matrix

	HOMO	LUMO	CMA	CSEV	LOGP	DDE	MR	VDW	NVDW	CAA	BS	SA	EC	KP
HOMO	1.000													
LUMO	0.420	1.000												
CMA	0.130	0.350	1.000											
CSEV	0.229	0.399	0.980	1.000										
LOGP	0.740	0.523	0.562	0.675	1.000									
DDE	0.540	0.155	0.136	0.208	0.306	1.000								
MR	0.430	0.456	0.910	0.956	0.772	0.392	1.000							
VDW	0.287	0.629	0.361	0.304	0.129	0.070	0.221	1.000						
NVDW	0.467	0.081	0.557	0.441	0.206	0.212	0.284	0.487	1.000					
CAA	0.103	0.342	0.967	0.910	0.470	0.122	0.855	0.371	0.640	1.000				
BS	0.723	0.464	0.579	0.673	0.894	0.624	0.797	0.031	0.158	0.520	1.000			
SA	0.795	0.465	0.548	0.644	0.923	0.523	0.785	0.066	0.215	0.488	0.915	1.000		
EC	0.820	0.496	0.493	0.605	0.916	0.522	0.764	0.103	0.245	0.422	0.880	0.985	1.000	
KP	0.811	0.490	0.503	0.615	0.934	0.478	0.764	0.105	0.256	0.428	0.877	0.984	0.996	1.000

BS, *B. subtilis*; SA *S. aureus*; EC, *E. coli*; KP, *K. pneumoniae*

synthesized compounds. In terms of the % contribution of these physiochemical factors to the antibacterial profile of the compounds, LOGP has 83.6% contribution to the model, whereas the contribution of DDE term is only 16.4%. PRESS (predicted residual sum of squares) is a cross validation parameter whose value less than SSY (sum of the squares of response value) points out that the model predicts better than chance and can be considered statistically important. Further, to be a reasonable QSAR model PRESS/SSY ratio should be smaller than 0.4 and its value smaller than 0.11 indicates an excellent model. In our proposed model this ratio is 0.056, indicating that the proposed QSAR model is better model. Moreover, the predictive power of all above models has been proved by employing the leave-one-out (LOO) method. The value of cross-validated correlation coefficient (r^2_{cv}) and bootstrapping r^2 are further supporting the predictive power of these explaining models. Also, the whole data set was divided into two groups; one is training set containing 12 compounds and another is test set containing 4 compounds. The predicted activities for the test set (i.e., compounds **12b**, **12f**, **12k**, **12n**) for bacteria *B. subtilis* are −1.046, −1.385, −2.226, and −2.532, respectively. The value of r^2_{pred} for this bacterium for the test set is found to be 0.778. Furthermore, the studies were extended to propose the QSAR behavior of the synthesized compounds against *S. aureus*, *E. coli*, and *K. pneumoniae*. The result for another Gram positive bacteria *S. aureus* is presented in Eq. 2.

QSAR equations for antibacterial profile against *S. aureus*

$$\mathrm{pIC_{50}} = [-9.459(\pm 1.201)] + \mathrm{LOGP}[1.340(\pm 0.153)] + \mathrm{DDE}[0.157(\pm 0.077)] \quad (2)$$

Contribution of parameters to model is LOGP:DDE::9.01955:1

$n = 12$, $r = 0.993$, $r^2 = 0.986$, variance = 0.011, $S = 0.104$, $F = 308.102$, PRESS = 0.097, SSY = 6.759, PRESS/SSY = 0.014, $r^2_{cv} = 0.985$, % EV = 98.416, SEE = 0.090, Bootstrapping $r^2 = 0.987$, Bootstrapping $S = 0.007$, $Q^2 = 0.976$, $S_{PRESS} = 0.134$, SDEP = 0.116.

Equation 2 explains up to 98.42% of the variation of the activities of the compounds against *S. aureus*. The predicted activities for the test set for bacteria *S. aureus* are −1.212, −1.566, −2.093, and −2.627, respectively. The value of r^2_{pred} for this bacterium for the test set is found to be 0.703.

QSAR equations for antibacterial profile against *E. coli*

$$\mathrm{pIC_{50}} = [-8.634(\pm 1.449)] + \mathrm{LOGP}[1.207(\pm 0.185)] + \mathrm{DDE}[0.188(\pm 0.092)] \quad (3)$$

Contribution of parameters to model is LOGP:DDE::6.8079:1

$n = 12$ $r = 0.988$, $r^2 = 0.976$, variance = 0.016, $S = 0.125$, $F = 186.495$, PRESS = 0.141, SSY = 6.005, PRESS/SSY = 0.023, $r^2_{cv} = 0.976$, % EV = 97.408, SEE = 0.141, Bootstrapping $r^2 = 0.983$, Bootstrapping $S = 0.015$, $Q^2 = 0.937$, $S_{PRESS} = 0.205$, SDEP = 0.178.

The predicted activities for the test set for bacteria *E. coli* are −1.455, −1.711, −2.372, and −2.769, respectively. The value of r^2_{pred} for this bacterium for the test set is found to be 0.687.

QSAR equations for antibacterial profile against *K. pneumoniae*

$$\mathrm{pIC_{50}} = [-9.304(\pm 1.287)] + \mathrm{LOGP}[1.254(\pm 0.164)] + \mathrm{DDE}[0.126(\pm 0.082)] \quad (4)$$

Contribution of parameters to model is LOGP:DDE::10.5484:1

$n = 12$, $r = 0.990$, $r^2 = 0.980$, variance = 0.012, $S = 0.111$, $F = 227.019$, PRESS = 0.112, SSY = 5.744, PRESS/SSY = 0.019, $r^2_{cv} = 0.980$, % EV = 97.861, SEE = 0.112 Bootstrapping $r^2 = 0.985$, Bootstrapping $S = 0.013$, $Q^2 = 0.937$, $S_{PRESS} = 0.199$, SDEP = 0.173.

The predicted activities for the test set for bacteria *K. pneumoniae* are −1.469, −1.801, −2.237, and −2.775, respectively. The value of r^2_{pred} for this bacterium for the test set is found to be 0.724.

The F value obtained in Eqs. 1–4 is found statistically significant at 99% level. Similarly, cross-validated and leave-one-out (LOO) predicted activities explain variation of activities with physiochemical descriptors LOGP and DDE. In all above equations, (except Eq. 1) the value of $r^2 > 0.976$ and $r^2_{cv} > 0.976$, indicating significance of proposed models. For Eq. 1 the value of r^2 and r^2_{cv} is in the range to explain the significance of model up to considerable extent. Experimentally observed, calculated, and LOO predicted activities are shown in Table 4. The calculated and predicted activities of the synthesized compounds were in accordance with the observed activities as shown in Fig. 2.

Results and discussion

Preliminary experiments were carried out to determine the antibacterial activities of titled compounds **12a**–**p** in vitro against (i) Gram positive bacteria:(*B. subtilis* and *S. aureus*) and (ii) Gram negative bacteria: (*E. coli* and *K. pneumoniae*). Nutrient agar media was employed for bacterial growth and inocula containing approximately

Table 4 Experimentally calculated and LOO predicted activities of training set compounds against Gram positive and Gram negative bacteria

Entry	R	*B. subtilis*		*S. aureus*		*E. coli*		*K. pneumoniae*	
		pIC_{50}		pIC_{50}		pIC_{50}		pIC_{50}	
		Calculated	LOO predicted	Calculated	LOO predicted	Calculated	LOO predicted	Calculated	LOO predicted
12a	–H	−2.40082	−2.38356	−2.47719	−2.46025	−2.64076	−2.64113	−2.63245	−2.63101
12c	5-Cl	−2.88031	−2.82282	−2.98119	−2.94099	−3.08961	−3.0722	−3.10654	−3.08545
12d	5-OH	−2.86402	−2.85404	−2.97181	−2.98735	−3.0784	−3.10189	−3.09903	−3.11049
12e	6-OH	−1.02199	−0.96975	−1.19814	−1.16862	−1.43908	−1.47585	−1.4583	−1.49168
12g	6-Br	−1.82432	−1.85078	−1.86139	−1.86654	−2.09595	−2.03161	−2.05152	−2.03191
12h	5-Br	−1.8279	−1.9545	−1.86346	−1.91591	−2.09842	−2.11673	−2.05317	−2.03919
12i	5-CH_3	−2.78104	−2.76418	−2.92401	−2.92946	−3.02135	−3.01313	−3.06078	−3.06177
12j	6-CH_3	−2.63814	−2.70845	−2.84169	−2.86499	−2.92308	−2.94287	−2.99491	−3.02671
12l	4-OH	−2.3844	−2.40861	−2.54165	−2.55089	−2.66812	−2.66685	−2.707	−2.70529
12m	7-OH	−1.89349	−1.84331	−1.90124	−1.90047	−2.14352	−2.14244	−2.0834	−2.07619
12o	H-4Br	−0.73857	−0.62111	−1.03487	−1.01504	−1.24419	−1.3184	−1.32765	−1.40927
12p	H-7Br	−0.48601	−0.73431	−0.88938	−0.94894	−1.07052	−0.82293	−1.21123	−0.93776

10^7 CFUs/ml of bacteria were prepared from broth culture in log phase. Bacterial plate was incubated at 37°C for 24 h. The biological activities (pIC_{50}s), the lowest concentration (μg/ml) of the test compound that resulted no visible growth on the plates were recorded. DMSO was used as the solvent control to ensure that solvent had no bad effect on bacterial growth.

Interpretation of QSAR model reveals that only, partition coefficient and dipole–dipole energy exhibited ($r^2 > 0.91$) a good correlation with biological activity. Further, a close inspection of screening results reveals that the substitution in phenyl ring of 2-aminobenzathiazole nucleus exerted significant influence on the antibacterial armament. It is observed from the data that the compounds **12b**, **12e**, **12f**, **12o**, and **12p** possessing electron-attracting group, i.e., Br and Cl are found remarkably more active. However, presence of electron releasing groups decreases the activity of the synthesized compounds. The fairly high positive coefficient of log P suggests that increase in the hydrophobicity of the molecule increases the antibacterial activity. This is in good agreement with our experimental finding. Moreover, it is evident from proposed QSAR studies that the rise in dipole–dipole energy (DDE) increases the antibacterial profile of synthesized compounds. LOG P and DDE parameters were the main governing physicochemical factors for the displayed antimicrobial activities. Such a QSAR evaluation would open up future perspectives to use these compounds as new lead compounds in clinical trials.

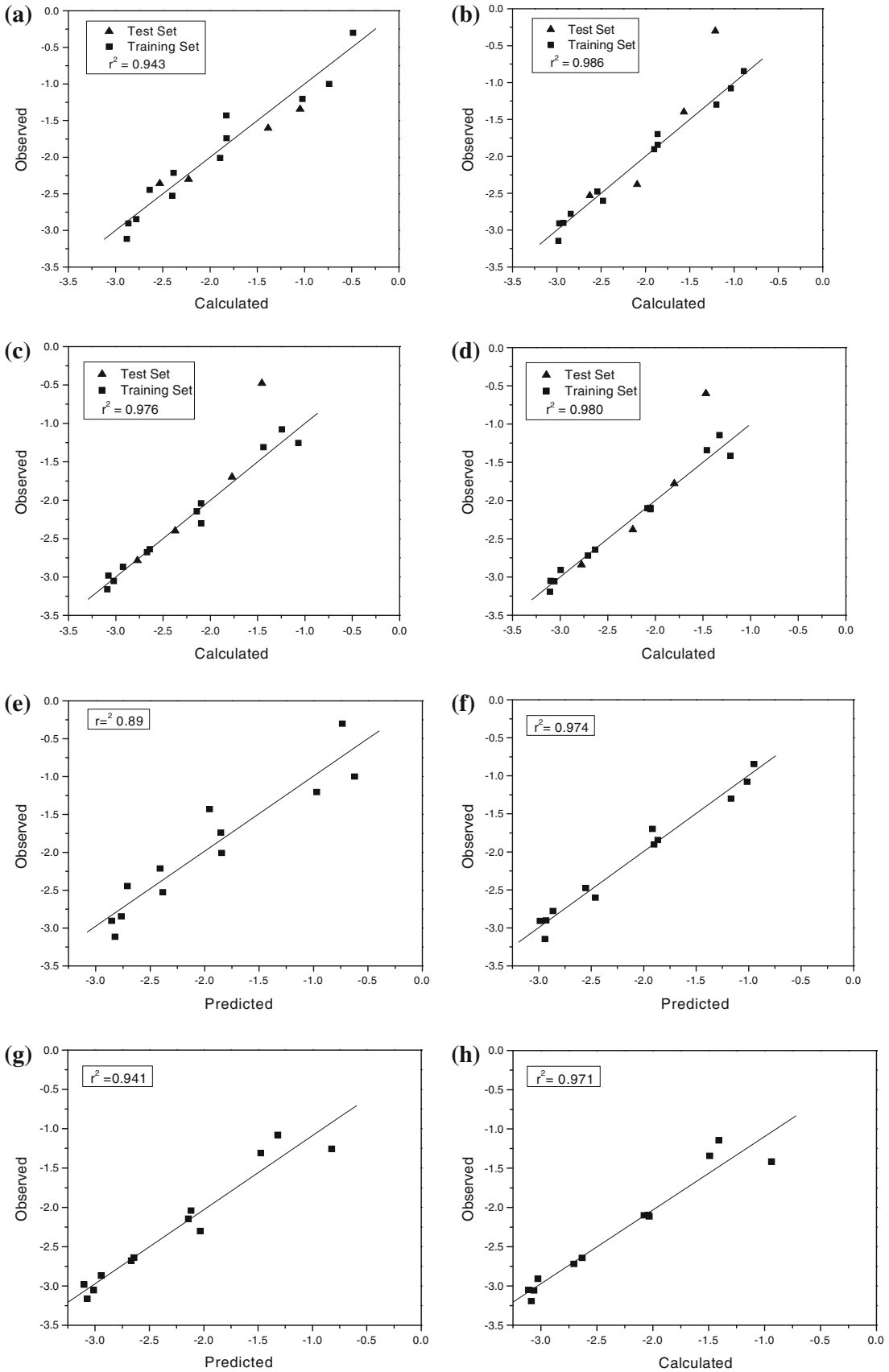
Experimental

All the chemicals used were of AR grade purity. Melting points were taken in open capillary tubes using an electric melting point apparatus. All the reported melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz with a Bruker advance DRX 300 instrument using TMS as an internal stranded. IR spectra were run on a Perkin Elmer model 377-spectrophotometer using KBr pellets. Analytical thin layer chromatography was performed using E. Merck Silica gel 0.50 mm plate (Merck No. 5700).

Preparation of 1,3-benzothiazol-2-amine (**4**): general procedure

A mixture of pertinently substituted aniline (0.1 M), conc. HCl (9.0 ml) and water (25 ml) were taken in a 250 cc round bottomed flask and contents were refluxed for half an hour. The solution was cooled at room temperature and ammonium thiocyanate (7.6 g, 0.1 M) was added. The reaction mixture was then refluxed for 4 h till two layers were separated out. The solution was poured into crushed ice and was filtered, dried, and crystallized from ethanol to yield the crystals of aryl thiourea (**2**).

In a 500 ml two-necked R.B. flask equipped with mechanical stirrer, appropriately substituted aryl thiourea (**2**) (0.1 M) was dissolved in chloroform (100 ml). Now bromine (0.1 M) in chloroform (50 ml) was taken in a dropping funnel and was added drop wise with stirring to the reaction mixture by maintaining the temperature below 5°C. After the complete addition of bromine, the stirring was continued for a period of 3–4 h and the contents of the flask were refluxed on water bath till the evolution of hydrogen bromide vapors ceased. The resulting solid material was treated with aqueous sulfur dioxide solution and filtered. The filtrate was neutralized with aqueous ammonia solution and the precipitate


(a)
Test Set
Training Set
r² = 0.943
Observed
Calculated
(b)
Test Set
Training Set
r² = 0.986
Observed
Calculated
(c)
Test Set
Training Set
r² = 0.976
Observed
Calculated
(d)
Test Set
Training Set
r² = 0.980
Observed
Calculated
(e)
r=² 0.89
Observed
Predicted
(f)
r²= 0.974
Observed
Predicted
(g)
r² =0.941
Observed
Predicted
(h)
r²= 0.971
Observed
Calculated

◀**Fig. 2** **a**–**d** Plots of observed vs. calculated activities for test and training set of 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones (**12a**–**p**) against *B. subtilis*, *S. aureus*, *E. coli*, and *K. pneumoniae*, respectively. **e**–**h** Plots of observed vs. LOO-predicted antibacterial activities of 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones (for training set) against *B. subtilis*, *S. aureus*, *E. coli*, and *K. pneumoniae*, respectively

obtained was filtered and washed with water and crystallized from ethanol. Thus, colored crystals of 1,3-benzothiazol-2-amine (**4**) were obtained in good yields (60–75%).

*1,3-Benzothiazol-2-amine (**4a**)*

Yield 75%; mp. 112–113°C; Anal Calcd for $C_7H_6N_2S$: C, 55.94; H, 4.00; N, 18.61%; Found: C, 55.97; H, 3.96; N, 18.55%; IR (ν, cm^{-1}): 3253 (–NH), 3052 (C–H, sp^2), 1605, 1495, 1395 (C···C, ring str.), 1575 (C=C/C=N); ^{1}HNMR (δ ppm): 5.0 (s, 2H, $–NH_2$), 7.52–8.20 (m, 4*H*, Ar–H); FAB-Mass: 151 (M^++1).

Compounds (**4a**–**o**) were synthesized by taking different substituted anilines at 4, 5, 6 and 7 positions. The spectral analyses of synthesized compounds are as follows:

*5-Chloro-1,3-benzothiazol-2-amine(**4b**)*

Yield 62%; mp. 136–137°C; Anal Calcd for $C_7H_5ClN_2S$: C, 45.53; H, 2.73; N, 15.17%; Found: C, 55.97; H, 3.96; N, 18.55%; IR (ν, cm^{-1}): 3260 (–NH), 3058 (C–H, sp^2), 1608, 1490, 1392 (C···C, ring str.), 1578 (C=C/C=N), 550 (C–Cl); ^{1}HNMR (δ ppm): 5.10 (s, 2H, $–NH_2$), 7.66–8.38 (m, 3H, Ar–H); FAB-Mass: 185 (M^++1).

*5-Hydroxy-1,3-benzothiazol-2-amine(**4c**)*

Yield 62%; mp. 120–122°C; Anal Calcd for $C_7H_6N_2OS$: C, 50.59; H, 3.64; N, 16.86%; Found: C, 50.47; H, 3.63; N, 16.43%; IR (ν, cm^{-1}): 3362(–OH), 3256 (–NH), 3050 (C–H, sp^2), 1602, 1498, 1402 (C···C, ring str.), 1568 (C=C/C=N); ^{1}HNMR (δ ppm): 5.08 (s, 2H, $–NH_2$), 7.18–8.38 (m, 3H, Ar–H), 10.52 (s, 1H, –OH); FAB-Mass: 167 (M^++1).

*6-Hydroxy-1,3-benzothiazol-2-amine(**4d**)*

Yield 66%; mp. 117–118°C; Anal Calcd for $C_7H_6N_2OS$: C, 50.59; H, 3.64; N, 16.86%;O, 9.63; Found: C, 50.61; H, 3.65; N, 16.59%; IR (ν, cm^{-1}): 3355(–OH), 3253 (–NH), 3054 (C–H, sp^2), 1600, 1495, 1405 (C···C, ring str.), 1565 (C=C/C=N); ^{1}HNMR (δ ppm): 5.07 (s, 2H, $–NH_2$), 7.14–8.56 (m, 3H, Ar–H), 10.22 (s, 1H, –OH); FAB-Mass: 167 (M^++1).

*6-Bromo-1,3-benzothiazol-2-amine(**4e**)*

Yield 73%; mp. 134–135°C; Anal Calcd for $C_7H_5BrN_2S$: C, 36.20; H, 2.20; N, 12.23%; Found: C, 55.97; H, 3.96; N, 18.55%; IR (ν, cm^{-1}): 3254 (–NH), 3048 (C–H, sp^2), 1625, 1493, 1404 (C···C, ring str.), 1558 (C=C/C=N), 607 (C–Br); ^{1}HNMR (δ ppm): 5.10 (s, 2H, $–NH_2$), 7.83–8.46 (m, 3H, Ar–H); FAB-Mass: 230 (M^++1).

*5-Bromo-1,3-benzothiazol-2-amine(**4f**)*

Yield 67%; mp. 144–145°C; Anal Calcd for $C_7H_5BrN_2S$: C, 36.20; H, 2.20; N, 12.23%; Found: C, 36.16; H, 2.17; N, 12.28%; IR (ν, cm^{-1}): 3250 (–NH), 3046 (C–H, sp^2), 1622, 1498, 1398 (C···C, ring str.), 1562 (C=C/C=N), 609 (C–Br); ^{1}HNMR (δ ppm): 5.12 (s, 2H, $–NH_2$), 7.92–8.46 (m, 3H, Ar–H); FAB-Mass: 230 (M^++1).

*5-Methyl-1,3-benzothiazol-2-amine(**4g**)*

Yield 65%; mp. 132.5–133.5°C; Anal Calcd for $C_8H_8N_2S$: C, 58.51; H, 4.91; N, 17.06%; Found: C, 58.49; H, 4.88; N, 17.01%; IR (ν, cm^{-1}):3259 (–NH), 3058 (C–H, sp^2), 2872(C–H, sp^3),1608, 1502, 1392 (C···C, ring str.), 1568 (C=C/C=N); ^{1}HNMR (δ ppm): 2.46 (s, 3H, $–CH_3$), 5.08 (s, 2H, $–NH_2$), 7.68–8.20 (m, 3H, Ar–H); FAB-Mass: 165 (M^++1).

*6-Methyl-1,3-benzothiazol-2-amine(**4h**)*

Yield 61%; mp. 138.5–139.5°C; Anal Calcd for $C_8H_8N_2S$: C, 58.51; H, 4.91; N, 17.06; Found: C, 58.42; H, 4.89; N, 16.98; IR (ν, cm^{-1}):3257 (–NH), 3055 (C–H, sp^2), 2878(C–H, sp^3),1605, 1500, 1390 (C···C, ring str.), 1574 (C=C/C=N); ^{1}HNMR (δ ppm): 2.42 (s, 3H, $–CH_3$), 5.12 (s, 2H, $–NH_2$), 7.98–8.36 (m, 3H, Ar–H); FAB-Mass: 165 (M^++1).

*6-Hydroxy-1,3-benzothiazol-2-amine(**4i**)*

Yield 68%; mp. 119–120°C; Anal Calcd for $C_7H_6N_2OS$: C, 50.59; H, 3.64; N, 16.86%; Found: C, 50.57; H, 3.96; N, 16.79%; IR (ν, cm^{-1}): 3350(–OH), 3255 (–NH), 3054 (C–H, sp^2), 1600, 1495, 1405 (C···C, ring str.), 1565 (C=C/C=N); ^{1}HNMR (δ ppm): 5.01 (s, 2H, $–NH_2$), 7.12–8.18 (m, 3H, Ar–H); 10.45 (s, 1H, –OH), FAB-Mass: 167 (M^++1).

*7-Hydroxy-1,3-benzothiazol-2-amine(**4j**)*

Yield 69%; mp. 124–125°C; Anal Calcd for $C_7H_6N_2OS$: C, 50.59; H, 3.64; N, 16.86%; Found: C, 50.47; H, 3.62; N, 16.81%; IR (ν, cm^{-1}): 3354(–OH), 3253 (–NH), 3052

(C–H, sp^2), 1600, 1495, 1405 (C=C, ring str.), 1565 (C=C/C=N); ^{1}HNMR (δ ppm): 5.02 (s, 2H, $–NH_2$), 7.15–8.25 (m, 3H, Ar–H), 10.32 (s, 1H, –OH); FAB-Mass: 167 (M^++1).

*5-Methoxy-1,3-benzothiazol-2-amine(**4k**)*

Yield 73%; mp. 146–147°C; Anal Calcd for $C_8H_8N_2OS$: C, 53.51; H, 4.47; N, 15.54%; Found: C, 53.42; H, 4.44; N, 15.45%; IR (ν, cm^{-1}): 3255 (–NH), 3045 (C–H, sp^2), 2870(C–H, sp^3),1615, 1490, 1395 (C=C, ring str.), 1575 (C=C/C=N), 2826 (OCH_3); ^{1}HNMR (δ ppm): 3.73 (s, 3H, $–CH_3$), 5.14 (s, 2H, $–NH_2$), 7.26–8.12 (m, 3H, Ar–H); FAB-Mass: 181 (M^++1).

*4-Methoxy-1,3-benzothiazol-2-amine(**4l**)*

Yield 70%; mp. 149–150°C; Anal Calcd for $C_8H_8N_2OS$: C, 53.51; H, 4.47; N, 15.54%; Found: C, 53.48; H, 4.39; N, 15.43%; IR (ν, cm^{-1}): 3250 (–NH), 3048 (C–H, sp^2), 2854 (C–H, sp^3),1612, 1490, 1395 (C=C, ring str.), 1578 (C=C/C=N); ^{1}HNMR (δ ppm): 3.83 (s, 3H, $–CH_3$), 5.10 (s, 2H, $–NH_2$), 7.28–7.88 (m, 3H, Ar–H); FAB-Mass: 181 (M^++1).

*4-Methyl-1,3-benzothiazol-2-amine(**4m**)*

Yield 60%; mp. 136.5–137.5°C; Anal Calcd for $C_8H_8N_2S$: C, 58.51; H, 4.91; N, 17.06%; Found: C, 58.48; H, 4.90; N, 16.99%; IR (ν, cm^{-1}): 3257 (–NH), 3055 (C–H, sp^2), 2864(C–H, sp^3),1605, 1500, 1390 (C=C, ring str.), 1570 (C=C/C=N); ^{1}HNMR (δ ppm): 2.52 (s, 3H, $–CH_3$), 5.06 (s, 2H, $–NH_2$), 7.65–8.22 (m, 3H, Ar–H); FAB-Mass: 165 (M^++1).

*7-Methyl-1,3-benzothiazol-2-amine(**4n**)*

Yield 63%; mp. 142.5–143.5°C; Anal Calcd for $C_8H_8N_2S$: C, 58.51; H, 4.91; N, 17.06%; Found: C, 58.42; H, 4.87; N, 17.03; IR (ν, cm^{-1}):3257 (–NH), 3052 (C–H, sp^2), 2860(C–H, sp^3),1605, 1500, 1390 (C=C, ring str.), 1572(C=C/C=N); ^{1}HNMR (δ ppm): 2.45 (s, 3H, $–CH_3$), 5.09 (s, 2H, $–NH_2$), 7.65–8.24 (m, 3H, Ar–H); FAB-Mass: 165 (M^++1).

*4-Bromo-1,3-benzothiazol-2-amine(**4o**)*

Yield 72%; mp. 134–135°C; Anal Calcd for $C_7H_5BrN_2S$: C, 36.20; H, 2.20; N, 12.23%; Found: C, 36.18; H, 2.16; N, 12.15%; IR (ν, cm^{-1}): 3252 (–NH), 3048 (C–H, sp^2), 1620, 1495, 1402 (C=C, ring str.), 1555 (C=C/C=N), 608 (C–Br); ^{1}HNMR (δ ppm): 5.10 (s, 2H, $–NH_2$), 7.80–8.34 (m, 3H, Ar–H); FAB-Mass: 230 (M^++1).

*7-Bromo-1,3-benzothiazol-2-amine(**4p**)*

Yield 75%; mp. 148–149°C; Anal Calcd for $C_7H_5BrN_2S$: C, 36.20; H, 2.20; N, 12.23%; Found: C, 55.97; H, 3.96; N, 18.55%; IR (ν, cm^{-1}): 3250 (–NH), 3052 (C–H, sp^2), 1622, 1495, 1402 (C=C, ring str.), 1557 (C=C/C=N), 607 (C–Br); ^{1}HNMR (δ ppm): 5.07 (s, 2H, $–NH_2$), 7.74–8.44 (m, 3H, Ar–H); FAB-Mass: 230 (M^++1).

Synthesis of 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3H)-ones via 2-amino-5-[(E)-phenyl diazenyl] benzoic acid as precursors (Route A)

5.0 g (4.9 ml, 0.054 mol) of aniline was dissolved in a mixture of 14.0 ml HCl and 14.0 ml of water in a 250 ml round bottom flask. The flask was immersed in a bath of crushed ice and salt mixture was cooled until the temperature of the stirred solution was fallen below 5°C. Further, 3.47 g (0.05 mol) of sodium nitrite was dissolved in 17.0 ml of water and the solution was chilled by immersion in the ice bath. The sodium nitrite solution was added in small volumes to the cold aniline hydrochloride solution through shaking. The last 5% of sodium nitrite solution was added more slowly after shaking for 3–4 min. Meanwhile 7.5 g (0.05 mol) of anthranilic acid was dissolved in 75.0 ml of 2 M-hydrochloric acid in a 600 ml beaker, the reaction mixture was cooled and to this benzenediazonium chloride solution was added rapidly and with vigorous stirring. Then sodium acetate solution (25.0 g of the trihydrate in 12.5 ml of water) was added slowly and with stirring until precipitation of the dyestuff was complete, stirring was continued for 1 h. The solution was heated and filtered through the heated funnel. 50.0 g of sodium chloride was added to the filtrate and was heated on the steam bath until the precipitated dyestuff appeared crystalline. The yield of 2-amino-5-[(*E*)-phenyl diazenyl] benzoic acid (6) was 71%.

0.05 mol of phosphorous pentachloride was added in 12.05 g (0.05 mol) of 2-amino-5-[(*E*)-phenyl diazenyl] benzoic acid to give compound **6**. Further equimolar quantities of compound **6** (0.05 mol) and 2-aminobenzothiazole were taken in 12.0 ml of pyridine and were refluxed for 4 h to give compound **7** which was further benzoylated using (.05 mol) benzoyl chloride followed by dehydration in dry pyridine at 0–5°C for 3 h to give compound **10**. Compound **10** was treated with 0.114 molar aqueous solution of sodium dithionite with continuous stirring which discharges the color and resulted the finely divided precipitate of compound **11**. (0.03 mol) compound **11** was dissolved by heating on water bath with 60 ml of rectified spirit and 15 ml of benzene in a 200-ml two-necked flask fitted with reflux condenser, the

second neck being closed with stopper. 5.30 g (3.5 ml) of concentrated sulfuric acid was added to the hot solution of compound **11** via the side neck through graduated pipette and the liquid was gently swirled, the stopper was replaced and the solution was heated on the water bath until the clear solution was boiled. The flask was removed from the water bath and 3.5 g (0.05 mol) of powdered sodium nitrite was added in two approximately equal portions via the side neck; after each addition, the stopper was replaced and the flask was shaken vigorously; when the reaction was subsided, the second portion of sodium nitrite was added. The flask was heated on the water bath as long as the gas evolved with shaking from time to time. Further, the solution was cooled for 10 min, and then the flask was immersed in the ice bath. Furthermore, a mixture of compound **12** and sodium sulfate was crystallized out. The solution was filtered with suction on buchner funnel and was washed with a small quantity of ethanol and then repeatedly with water to remove all the sodium sulfate. The crude 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-one (7.5 g) was dissolved in a boiling mixture of 120 ml of glacial acetic acid and 30 ml of water, the solution was boiled with 2.5 g of activated charcoal and was filtered through a hot water funnel; the solution was allowed to cool on a buchner funnel and washed with a small quantity of chilled rectified spirit to remove the acetic acid. The crystals were dried in the air upon filter paper to yield the desired titled compounds.

Synthesis of 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones via 2-phenyl-4*H* benzo[d] [1,3] oxazin-4-one as precursors (Route B)

Preparation of 2-phenyl-4*H* benzo[d] [1,3] oxazin-4-one(15)

The mixture of anthranilic acid (0.246 mol) with 50.0 ml absolute ethanol and 2.5 ml concentrated sulfuric acid was refluxed for 4 h, to give ethyl anthranilate. The mixture of ethyl anthranilate (0.01 mol) with 100 ml absolute ethanol and benzoic anhydride (0.01 mol) was refluxed further for 48 h to form compound **15**. The reaction mixture was neutralized with saturated sodium bicarbonate solution and the pale yellow solid which separated was filtered, washed with water and recrystallised from ethanol.

Yield 83%, mp. 113–115°C (lit [20] 114°C); Anal Calcd for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3030 (C–H, Ar–H), 1725 (C=O), 1595 (C=N), 1180 (C–O) cm^{-1}; ^{1}HNMR: δ 7.61 (m, 9H, Ar–H,); FAB-Mass: 225 (M^++1).

Preparation of 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-ones (**12a**–**p**)

An equimolar mixture (0.01 mol) of 2-phenyl-4*H* benzo[d] [1,3] oxazin-4-one and benzothiazole-2-amine derivatives was taken, mechanistically stirred and the mixture was refluxed for 6 h in the presence of 10 ml of pyridine. Upon cooling, the mixture was poured onto crushed ice. The precipitated solid was collected and crystallized from ethanol to give the desired titled compounds.

Yield 78%, mp. 274–276°C (lit [20] 114°C); Anal Calcd for $C_{21}H_{13}N_3OS$: C, 70.97; H, 3.69; N, 11.82%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3025 (C–H, Ar–H), 1721 (C=O), 1620 (C=N quinazoline), 1185 (C–O) cm^{-1}; ^{1}HNMR: δ 7.42–8.38 (m, 13*H*, Ar–H,), FAB-Mass: 356 (M^++1).

Compounds (**12a**–**p**) were synthesized by condensing different substituted benzothiazoles with 2-phenyl-4*H* benzo[d] [1,3] oxazin-4-one(6) at 4,5,6, and 7 positions. The spectral analyses data of synthesized compounds are as follows:

*3-(5-Chloro-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12b**)*

Yield 80%, mp. 196–198°C; Anal Calcd for $C_{21}H_{12}ClN_3OS$: C, 64.70; H, 3.10; N, 10.78%; Found: C, 64.66; H, 3.08; N, 10.74%; IR: *v* 3042 (C–H, Ar–H), 1719 (C=O), 1625 (C=N), 585 cm^{-1} (Ar–Cl); ^{1}HNMR: δ 7.48–8.34 (m, 12H, Ar–H,), FAB-Mass: 391 (M^++1).

*3-(5-Hydroxy-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12c**)*

Yield 79%, mp. 276–278°C; Anal Calcd for $C_{21}H_{13}N_3O_2S$: C, 67.91; H, 3.53; N, 11.31%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3363(–OH), 3040 (C–H, Ar–H), 1726 (C=O), 1621 (C=N), 1175 (C–O) cm^{-1}; ^{1}HNMR: δ 7.23–8.30 (m, 12H, Ar–H,), 5.54 (bs, 1H, –OH), FAB-Mass: 372 (M^++1).

*3-(6-Hydroxy-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12d**)*

Yield 80%, mp. 275–277°C; Anal Calcd for $C_{21}H_{13}N_3O_2S$: C, 67.91; H, 3.53; N, 11.31%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3357(–OH), 3032 (C–H, Ar–H), 1725 (C=O), 1622 (C=N), 1177 (C–O) cm^{-1}; ^{1}HNMR: δ 7.36–8.18 (m, 12H, Ar–H,), 5.40 (bs, 1H, –OH), FAB-Mass: 372 (M^++1).

*3-(6-Bromo-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12e**)*

Yield 81%, mp. 212–214°C; Anal Calcd for $C_{21}H_{12}B_rN_3OS$: C, 58.08; H, 2.78; N, 9.68%; Found: C,

55.97; H, 3.96; N, 18.55%; IR: *v* 3040 (C–H, Ar–H), 1723(C=O), 1618 (C=N), 612 cm^{-1}(C–Br); ^{1}HNMR: δ 7.52–8.28 (m, 12H, Ar–H,), FAB-Mass: 435 (M^++1).

*3-(5-Bromo-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12f**)*

Yield 80%, mp. 208–210°C; Anal Calcd for $C_{21}H_{12}B_rN_3OS$: C, 58.08; H, 2.78; N, 9.68%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3045 (C–H, Ar–H), 1716 (C=O), 1618 (C=N), 613 cm^{-1}(C–Br); ^{1}HNMR: δ 7.34–8.48 (m, 12H, Ar–H,), FAB-Mass: 435 (M^++1).

*3-(5-Methyl-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12g**)*

Yield 71%, mp. 178–180°C; Anal Calcd for $C_{22}H_{15}N_3OS$: C, 71.52; H, 4.09; N, 11.37%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3042 (C–H, Ar–H), 2871(C–H, sp^3),1729(C=O), 1626(C=N), 1374 cm^{-1} (C–H deformation); ^{1}HNMR: δ 2.45 (d, 3H, –CH_3), 7.39–8.33 (m, 12H, Ar–H,); FAB-Mass: 370 (M^++1).

*3-(6-Methyl-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12h**)*

Yield 72%, mp. 182–184°C; Anal Calcd for $C_{22}H_{15}N_3OS$: C, 71.52; H, 4.09; N, 11.37%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3043 (C–H, Ar–H), 2866(C–H, sp^3),1735 (C=O), 1624 (C=N), 1373 cm^{-1} (C–H deformation); ^{1}HNMR: δ 2.43 (d, 3H, –CH_3), 7.39–8.23 (m, 12H, Ar–H,); FAB-Mass: 370 (M^++1).

*3-(4-Hydroxy-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12i**)*

Yield 81%, mp. 278–280°C; Anal Calcd for $C_{21}H_{13}N_3O_2S$: C, 67.91; H, 3.53; N, 11.31%; Found: C, 67.85; H, 3.48; N, 11.09%; IR: *v* 3371(–OH), 3035 (C–H, Ar–H), 1725 (C=O), 1618 (C=N), 1178 (C–O) cm^{-1}; ^{1}HNMR: δ 7.22–8.12 (m, 12H, Ar–H,), 5.42 (bs, 1H, –OH), FAB-Mass: 372 (M^++1).

*3-(7-Hydroxy-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12j**)*

Yield 78%, mp. 268–270°C; Anal Calcd for $C_{21}H_{13}N_3O_2S$: C, 67.91; H, 3.53; N, 11.31%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3356(–OH), 3036 (C–H, Ar–H), 1715 (C=O), 1618 (C=N), 1181 (C–O) cm^{-1}; ^{1}HNMR: δ 7.18–8.22 (m, 12H, Ar–H,), 5.42 (bs, 1H, –OH), FAB-Mass: 372 (M^++1).

*3-(5-Methoxy-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12k**)*

Yield 75%, mp. 188–190°C; Anal Calcd for $C_{22}H_{15}N_3O_2S$: C, 68.55; H, 3.92; N, 10.90%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3035 (C–H, Ar–H), 2867(C–H, sp^3), 1722 (C=O), 1621 (C=N); ^{1}HNMR: δ 3.85 (s, 3H, –OCH_3), 7.29–8.21 (m, 12H, Ar–H,); FAB-Mass: 386 (M^++1).

*3-(4-Methoxy-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12l**)*

Yield 77%, mp. 214–216°C; Anal Calcd for $C_{22}H_{15}N_3O_2S$: C, 68.55; H, 3.92; N, 10.90%; Found: C, 68.41; H, 3.82; N, 10.53%; IR: *v* 3038(C–H, Ar–H), 2910(C–H, sp^3),1722 (C=O), 1620 (C=N); ^{1}HNMR: δ 3.82 (s, 3H, –OCH_3), 7.26–8.24 (m, 12H, Ar–H,); FAB-Mass: 386 (M^++1).

*3-(4-Methyl-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12m**)*

Yield 74%, mp. 150–152°C; Anal Calcd for $C_{22}H_{15}N_3OS$: C, 71.52; H, 4.09; N, 11.37%; Found: C, 70.98; H, 3.96; N, 11.25%; IR: *v* 3045 (C–H, Ar–H), 2869(C–H, sp^3), 1722 (C=O), 1628(C=N), 1376 cm^{-1} (C–H deformation); ^{1}HNMR: δ 2.48 (d, 3H, –CH_3), 7.36–8.42 (m, 12H, Ar–H,); FAB-Mass: 370 (M^++1).

*3-(7-Methyl-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12n**)*

Yield 69%, mp. 166–168°C; Anal Calcd for $C_{22}H_{15}N_3OS$: C, 71.52; H, 4.09; N, 11.37%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3042 (C–H, Ar–H), 2853(C–H, sp^3),1719 (C=O), 1623 (C=N), 1370 cm^{-1} (C–H deformation); ^{1}HNMR: δ 2.42 (d, 3H, –CH_3), 7.36–8.28 (m, 12H, Ar–H,); FAB-Mass: 370 (M^++1).

*3-(4-Bromo-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12o**)*

Yield 83%, mp. 206–208°C; Anal Calcd for $C_{21}H_{12}B_rN_3OS$: C, 58.08; H, 2.78; N, 9.68%; Found: C, 57.91; H, 2.73; N, 9.55%; IR: *v* 3042 (C–H, Ar–H), 1722 (C=O), 1618 (C=N), 612 cm^{-1}(C–Br); ^{1}HNMR: δ 7.35–8.24 (m, 12H, Ar–H,), FAB-Mass: 435 (M^++1).

*3-(7-Bromo-1,3-benzothiazol-2-yl)-2-phenylquinazolin-4(3H)-one (**12p**)*

Yield 82%, mp. 210–212°C; Anal Calcd for $C_{21}H_{12}B_rN_3OS$: C, 58.08; H, 2.78; N, 9.68%; Found: C, 55.97; H, 3.96; N, 18.55%; IR: *v* 3038 (C–H, Ar–H), 1724

(C=O), 1621 (C=N), 614 cm^{-1} (C–Br); ^{1}HNMR: δ 7.54–8.32 (m, 12H, Ar–H,), FAB-Mass: 435 (M^++1).

Conclusion

A number of new 3-(1,3-benzothiazol-2-yl) 2-phenyl quinazolin-4(3*H*)-one compounds were synthesized and screened for their inherent antibacterial potential. Outcome of the rigorous QSAR studies reveals that compounds **12b**, **12e**, **12f**, **12o**, and **12p** are identified as most potent antibacterial agents. In this regard contribution of LOG P and DDE parameters was found remarkably significant. Hence in view to cater the needs associated with ever increasing demand of newer antibacterial agents, exploration of these findings can envisage these compounds as powerful antibacterial agents.

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