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Synthesis, antimicrobial, and QSAR studies of substituted benzamides

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Abstract—A series of new substituted benzamides were synthesized and tested in vitro for their antibacterial activity against Gram-positive and Gram-negative bacteria and as well for antifungal activity. The compounds **8i** and **9** showed better activity among the different benzamides synthesized. The structural characteristics governing antibacterial activities of substituted benzamides were studied using QSAR methodology. The results showed that the antimicrobial activity could be modeled using the topological descriptors, molecular connectivity indices ($^2\chi^v$ and $^2\chi$) and Kiers shape index ($\kappa\alpha_1$). The low residual activity and high cross-validated r^2 values (r^2_{cv}) observed indicated the predictive ability of the developed QSAR models.

1. Introduction

Benzamides are important class of compounds that show various types of biological activities.[1–3] Oxyclozanide (Fig. 1) was reported as an antihelmintic agent effective against *Fasciola hepatica* for the treatment of liver fluke infection.[1] The synthesis of some *N*-(*o*-hydroxyphenyl)benzamides and phenylacetamides as possible metabolites of antimicrobial active benzoxazoles has been reported.[4] There is also a report of biological activity of benzamides as potent smooth muscle relaxant and potassium channel activators.[5]

Quantitative structure–activity relationship (QSAR) represents an attempt to relate structural descriptors of molecules with their physicochemical properties and biological activities. It is widely used for the prediction of physicochemical properties in chemical, environmental, and pharmaceutical areas.[6,7] The main steps implicated in this method include data collection, molecular descriptor selection and procurement, correlation model development, and finally model evaluation. At present, many types of molecular descriptors have been proposed to describe the structural features of the molecules.[8–10]

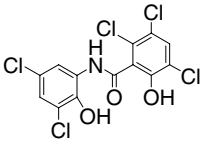

Figure 1. Structure of Oxyclozanide.

The success of QSAR approach can be explained by the insight offered into the structural determination of chemical properties, and the possibility to estimate the properties of new chemical compounds without the need to synthesize and test them.[11] Recently, we have reported the development of useful QSAR models for antimicrobial activity[12–15] and anti-inflammatory activity.[16]

In view of these observations and in continuation of our work related to the synthesis of bis(benzoxazole) natural product UK-1 and its aza-analogs possessing anticancer activity[17] which involves benzamides as intermediate, it was envisaged in the present investigation to undertake the synthesis and evaluation of antimicrobial activity of new substituted benzamides. Further, QSAR studies were carried out to find out the correlation between antimicrobial activities of synthesized benzamides with their physiochemical properties for the first time. Hansch analysis correlates biological activity values with electronic, steric, and hydrophobic influences of structural variance through linear regression analysis.

Keywords: Benzamides; Antimicrobial activity; QSAR; Topological descriptors.
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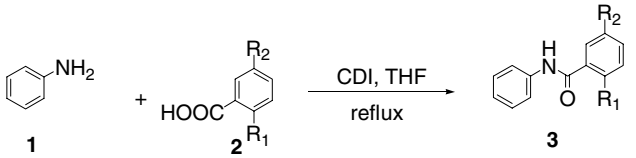
A series of new substituted benzamides (**3a**, **3b**, **7a**–**i**, **8a**–**i**, **9**, **14a**–**c**, **15a**–**c**, **16**) were synthesized by the reaction of substituted anilines with substituted aromatic acids in good to moderate yields using carbonyldiimidazole (CDI) in THF in one pot. This method is important because it does not require the protection and deprotection of hydroxyl group and conversion of acids to acid chlorides for further reaction in order to obtain benzamides.

The benzamides (**3a**–**e**) were prepared by the reaction of aniline (**1**) with substituted benzoic acids (**2**) (Scheme 1), whereas **7a**–**i** and **8a**–**i** were generated by the reaction of substituted benzoic acid (**4**) with 4-aminophenol (**5**) and 2-aminophenol (**6**), respectively (Scheme 2). However, **9** (Fig. 2) was prepared from 2-amino-3-carbmethoxyphenol and 2-benzyloxybenzoic acid.[17]

Further, reaction of substituted anilines (**10**) with 2-hydroxynaphthoic acid (**11**), 1-hydroxynaphthoic acid (**12**), and cinnamic acid (**13**) resulted in the formation of **14a**–**c**, **15a**–**c**, and **16**, respectively (Scheme 3). The structure of all the compounds was established by physical and spectroscopic methods (Table 1).

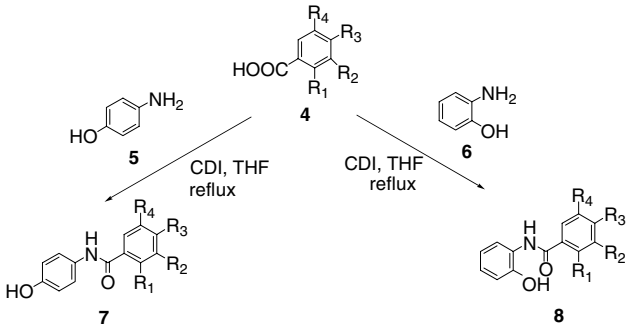
The substituted benzamides were evaluated for in vitro antibacterial activity against Gram-positive *Staphylococcus aureus* [MTCC 2901], *Bacillus subtilis*[MTCC 2063] and Gram-negative *Escherichia coli* [MTCC 1652], and in vitro antifungal activity against *Aspergillus ficcum* [MTCC 8184] and *Aspergillus parasiticus* [MTCC 8189]. Double strength nutrient broth-I.P. and Sabouraud dextrose broth-I.P.[18] were employed for bacterial and fungal growth, respectively. Minimum inhibitory concentrations were determined by means of standard serial dilution[19] and the −log MIC values are presented in Table 2. All the compounds exhibited appreciable in vitro activity against the tested strains compared to reference ciprofloxacin and salicylic acid in case of antibacterial and antifungal activity, respectively.

The compound **9** showed significant activity against *B. subtilis*, *E. coli*, and *A. ficcum* and *A. parasiticus*, whereas **8i** was most effective against *S. aureus*. Further, the antibacterial activity of compounds **3a**, **7g**–**i**, **8g**, **8i**, **14a**–**c**, **15b**, and **15c** was found to be more against *B. subtilis* having −log BS more than 1.20, than the other synthesized benzamides. Compounds **3a**, **3b**, **7e**–**i**, **8f**, **8g**, **8i**, **14a**, and **15b** were found to be more active against *S. aureus* having −log SA more than 1.30, than that of the other synthesized benzamides. Compounds **3a**, **7d**, **7g**–**i**, **8c**, **8g**, **9**, and **14a**–**c** were found to be more active against *E. coli* having −log EC more than 1.26, than the other synthesized benzamides. Moreover, the antifungal activity of compounds **3a**, **7e**–**g**, **8e**, **8f**, **8h**, **8i**, and **14a**–**c** was found to be more active against *A. ficcum* having



2a, 3a; $R_1 = OCH_2Ph$, $R_2 = H$
2b, 3b; $R_1 = Cl$, $R_2 = NO_2$

Scheme 1. Synthesis of substituted benzamides.



4a, 7a, 8a; $R_1, R_2, R_3, R_4 = H$
4b, 7b, 8b; $R_1 = OH$, $R_2, R_3, R_4 = H$
4c, 7c, 8c; $R_1, R_3, R_4 = H$, $R_2 = CH_3$
4d, 7d, 8d; $R_1, R_2, R_4 = H$, $R_3 = CH_3$
4e, 7e, 8e; $R_1, R_3, R_4 = H$, $R_2 = Cl$
4f, 7f, 8f; $R_2, R_3, R_4 = H$, $R_1 = Cl$
4g, 7g, 8g; $R_1, R_3, = H$, $R_2, R_4 = NO_2$
4h, 7h, 8h; $R_1 = Cl$, $R_2, R_3 = H$, $R_4 = NO_2$
4i, 7i, 8i; $R_1 = NO_2$, $R_2 = OCH_3$, $R_3, R_4 = H$

Scheme 2. Synthesis of *N*-(2/4-hydroxyphenyl) substituted benzamides.

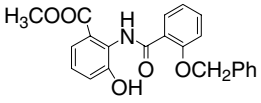
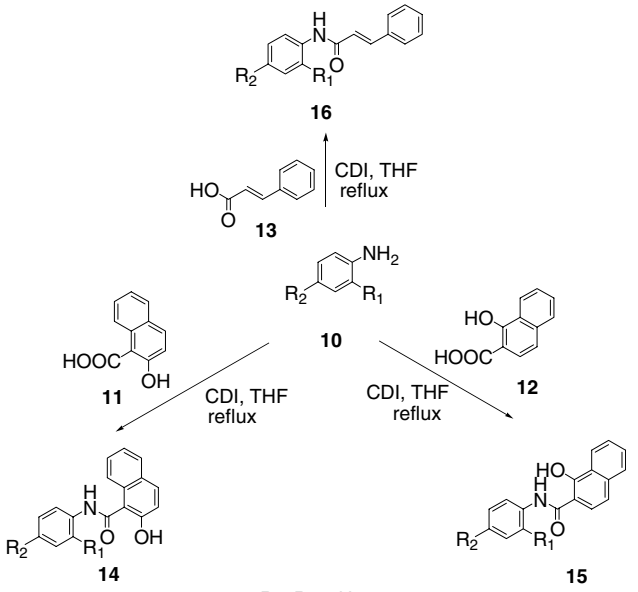


Figure 2. Structure of *N*-(2-carbmethoxy-6-hydroxyphenyl)-2-benzyloxybenzamide.



14a-15a; $R_1, R_2 = H$
14b-15b, **16**; $R_1 = H$, $R_2 = OH$
14c-15c; $R_1 = OH$, $R_2 = H$

Scheme 3. Synthesis of N-substituted naphthamides and 3-phenyl-propenoic amide.

Table 1. Physical and spectroscopic data of benzamides

Compound	Mp (°C)	Yield (%)	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)	Analytical data Calcd./ found
3a	107	64	3336, 1657, 1595, 1537, 1321	5.17 (s, 2H, OCH_2Ph), 7.00–7.02 (m, 1H), 7.08–7.26 (m, 6H), 7.44–7.51 (m, 6H), 8.32 (dd, J = 8.0, 1.8 Hz, 1H)	71.7, 112.5, 119.7, 121.7, 121.8, 123.7, 128.6, 128.7, 129.1, 132.6, 135.1, 138.5, 156.6, 162.9	$C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62% C, 79.00; H, 5.43; N, 4.51%
3b	133	66	3268, 1661, 1595, 1531, 1442, 1353, 1317, 1231	7.15 (t, J = 7.4 Hz, 1H), 7.33–7.37 (m, 3H), 7.62 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 6.9 Hz, 2H), 8.21 (dd, J = 8.7, 2.7 Hz, 1H)	119.8, 123.9, 124.2, 124.7, 128.4, 130.6, 137.1, 137.4, 137.8, 145.6, 162.5	$C_{13}H_9ClN_2O_3$: C, 56.43; H, 3.28; N, 10.13% C, 56.23; H, 3.02; N, 9.98%
7a	142	40	3228, 1684, 1649, 1536, 1512, 1324	6.82 (d, J = 8.6 Hz, 2H), 7.41–7.56 (m, 3H), 7.93 (d, J = 7.2 Hz, 2H), 8.04 (d, J = 7.2 Hz, 2H), 9.33 (br s, 1H)	115.0, 122.1, 122.1, 127.1, 127.8, 129.5, 130.1, 130.8, 132.2, 134.9, 165.5	$C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57% C, 73.00; H, 4.97; N, 6.39%
7b	152	50	3484, 3181, 1632, 1577, 1515, 1336, 1232	6.83–6.97 (m, 4H), 7.35–7.43 (m, 3H), 7.89 (dd, J = 8.0, 1.2 Hz, 1H), 8.77 (br s, 1H)	115.2, 117.5, 118.4, 121.7, 123.4, 127.2, 128.7, 135.4, 154.2, 160.3, 167.7	$C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11% C, 67.91; H, 4.68; N, 6.07%
7c	162	42	3321, 1686, 1588, 1513, 1414, 1311, 1214	2.40 (s, 3H, CH_3), 6.77 (m, 2H), 7.33–7.34 (m, 2H), 7.49–7.53 (m, 2H), 7.72–7.74 (m, 2H), 9.10 (br s, 1H)	115.3, 119.0, 121.5, 122.2, 126.4, 127.8, 128.1, 129.9, 130.1, 131.6, 133.0, 137.5, 168.3	$C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16% C, 73.74; H, 5.59; N, 6.07%
7d	190	48	3294, 1686, 1590, 1536, 1434, 1311, 1215	2.42 (s, 3H, CH_3), 6.18 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 9.12 (br s, 1H)	—	$C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16% C, 73.79; H, 5.60; N, 5.96%
7e	238	58	3330, 1647, 1517, 1256	6.15 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 8.30 (br s, 1H), 9.12 (br s, 1H)	114.8, 122.3, 127.8, 128.8, 130.0, 133.3, 136.5, 153.6, 164.2	$C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66% C, 62.85; H, 3.98; N, 5.41%
7f	178	61	3270, 1628, 1593, 1514, 1252	6.80 (d, J = 8.7 Hz, 2H), 7.31–7.43 (m, 3H), 7.49–7.55 (m, 3H), 8.79 (br s, 1H), 9.48 (br s, 1H)	115.0, 121.4, 126.4, 128.7, 129.4, 129.9, 130.2, 130.4, 136.5, 153.6, 164.5	$C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66% C, 62.91; H, 3.88; N, 5.53%
7g	263	57	3349, 1652, 1603, 1545, 1344, 1222	6.84 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 9.12 (s, 1H), 9.36 (s, 2H), 10.4 (br s, 1H)	114.9, 120.0, 122.4, 127.7, 129.1, 138.2, 147.8, 154.1, 160.2	$C_{13}H_9N_3O_6$: C, 51.49; H, 2.99; N, 13.86% C, 51.22; H, 2.78; N, 13.71%

(*continued on next page*)

Table 1 (*continued*)

Compound	Mp (°C)	Yield (%)	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)	Analytical data Calcd./ found
7h	230	65	3259, 1659, 1614, 1540, 1509, 1455, 1353, 1321, 1240	6.81 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 1H), 8.21 (dd, J = 8.7, 2.7 Hz, 1H), 8.39 (d, J = 2.7 Hz, 1H), 9.87 (br s, 1H)	115.0, 121.6, 123.8, 124.5, 129.4, 130.6, 137.4, 137.8, 145.5, 153.9, 162.2	$C_{13}H_9ClN_2O_4$: C, 53.35; H, 3.10; N, 9.57% C, 53.19; H, 2.96; N, 9.49%
7i	256	68	3502, 3443, 1653, 1540, 1480, 1338, 1262	3.96 (s, 3H, OCH_3), 6.84 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 7.1 Hz, 1H), 7.01 (t, J = 7.1 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.94 (d, J = 7.7 Hz, 1H)	56.3, 115.1, 115.5, 118.8, 119.1, 121.0, 125.0, 125.4, 129.8, 131.2, 139.0, 147.0, 150.7, 162.0	$C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72% C, 58.17; H, 4.02; N, 9.57%
8a	98	73	3297, 1645, 1616, 1551, 1455, 1240	7.33–7.36 (m, 2H), 7.49–7.53 (m, 3H), 7.56–7.59 (m, 1H), 7.75–7.79 (m, 1H), 8.24–8.27 (m, 2H)	110.6, 120.0, 124.6, 125.1, 127.1, 127.6, 128.9, 131.5, 142.1, 150.7, 163.0	$C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57% C, 73.05; H, 4.97; N, 6.51%
8b	158	69	3265, 1615, 1558, 1456, 1368, 1227	6.86–7.14 (m, 5H), 7.39 (t, J = 7.6 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H)	—	$C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11% C, 67.87; H, 4.65; N, 5.88%, 6.06%
8c	129	72	3416, 3094, 1645, 1540, 1455, 1281	2.32 (s, 3H, CH_3), 7.79 (t, J = 7.8 Hz, 1H), 6.88–6.98 (m, 2H), 7.21–7.28 (m, 2H), 7.61–7.66 (m, 2H), 7.76–7.82 (m, 1H), 8.95 (br s, 1H)	—	$C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16% C, 73.76; H, 5.69; N
8e	180	71	3388, 3094, 1652, 1590, 1539, 1453, 1283	6.87 (dd, J = 7.8, 1.4 Hz, 1H), 6.96 (dd, J = 8.0, 1.4 Hz, 1H), 7.00–7.04 (m, 1H), 7.44 (d, J = 8.5 Hz, 2 H), 7.91 (d, J = 8.5 Hz, 2H), 7.93–7.95 (m, 1H)	109.4, 116.1, 119.4, 121.2, 124.9, 125.9, 128.3, 128.5, 132.5, 137.3, 147.2, 164.5	$C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66% C, 62.89; H, 3.92; N, 5.46%
8f	171	71	3215, 1633, 1595, 1524, 1455, 1328, 1292	6.88–6.92 (m, 1H), 7.00–7.04 (m, 1H), 7.41–7.49 (m, 2H), 7.89–7.95 (m, 4H), 7.91 (m, 1H)	109.4, 116.1, 119.4, 121.2, 124.9, 125.9, 128.3, 128.5, 132.5, 137.3, 147.2, 164.5	$C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66% C, 62.94; H, 3.95; N, 5.40%
8g	126	65	3327, 1648, 1611, 1593, 1542, 1455, 1344, 1251	6.86 (d, J = 7.8 Hz, 1H), 7.01–7.04 (m, 1H), 7.41–7.47 (m, 2H), 9.12 (s, 1H), 9.35 (s, 2H), 10.4 (br s, 1H)	115.0, 120.6, 124.4, 127.8, 128.2, 138.0, 147.8, 154.4, 160.7	$C_{13}H_9N_3O_6$: C, 51.49; H, 2.99; N, 13.86% C, 51.34; H, 2.80; N, 13.65%
8h	170	80	3216, 1652, 1541, 1480, 1349, 1253	6.63–6.79 (m, 1H), 6.88–7.32 (m, 2H), 7.64 (d, J = 8.7 Hz, 1H), 8.07 (dd, J = 8.0, 1.4 Hz, 1H), 8.23 (dd, J = 8.7, 2.7 Hz, 1H), 8.56 (d, J = 2.7 Hz, 1H), 9.07 (br s, 1H)	109.2, 115.8, 119.7, 120.8, 121.5, 123.2 124.6, 125.3, 131.1, 136.4, 137.6, 145.9, 146.7, 162.2	$C_{13}H_9ClN_2O_4$: C, 53.35; H, 3.10; N, 9.57% C, 53.19; H, 2.97; N, 9.41%

Table 1 (*continued*)

Compound	Mp (°C)	Yield (%)	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)	Analytical data Calcd./ found
8i	241	60	3305, 1650, 1644, 1607, 1574, 1508, 1457, 1373, 1299	3.96 (s, 3H, OCH_3), 6.71–6.75 (m, 2H), 7.07 (d, J = 8.8 Hz, 1H), 7.18–7.20 (m, 2H), 7.40 (dd, J = 8.8, 8.2 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H)	—	$C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72% C, 58.20; H, 3.98; N, 9.62%
14a	136	52	3218, 1630, 1601, 1508, 1456, 1405, 1277, 1216	6.75–6.79 (m, 1H), 7.09–7.45 (m, 6H), 7.63 (d, J = 8.2 Hz, 1H), 7.65–7.77 (m, 3H)	—	$C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32% C, 77.36; H, 4.75; N, 5.09%
14b	149	50	3206, 1616, 1585, 1541, 1506, 1456, 1394, 1305, 1222	6.78 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.35–7.50 (m, 6H), 7.80 (d, J = 8.9 Hz, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.82 (br s, 1H), 9.51 (br s, 1H)	107.1, 115.1, 117.3, 122.1, 123.2, 123.9, 125.0, 125.1, 126.8, 128.3, 128.5, 135.7, 154.4, 160.3, 169.2	$C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02% C, 72.88; H, 4.48; N, 4.82%
14c	168	54	3219, 1630, 1601, 1512, 1456, 1405, 1362, 1277, 1216	6.90–7.02 (m, 3H), 7.31–7.35 (m, 1H), 7.57–7.79 (m, 4H), 8.07 (d, J = 8.0 Hz, 1H), 8.41 (d, J = 8.2 Hz, 1H), 9.40 (br s, 1H)		$C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02% C, 72.90; H, 4.48; N, 4.88%
15a	175	59	3354, 1615, 1541, 1508, 1448, 1298, 1240	6.72 (d, J = 7.4 Hz, 1H), 6.81 (t, J = 8.8, 0.8 Hz, 1H), 7.04–7.07 (m, 2H), 7.15–7.20 (m, 1H), 7.27–7.31 (m, 1H), 7.36–7.40 (m, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.68–7.74 (m, 2H)	—	$C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32% C, 77.39; H, 4.77; N, 5.14%
15b	180	52	3361, 1633, 1600, 1558, 1508, 1466, 1405, 1245	6.76 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.30–7.52 (m, 6H), 7.83 (d, J = 8.8 Hz, 1H), 8.32 (d, J = 8.2 Hz, 1H), 8.80 (br s, 1H), 9.40 (br s, 1H)	—	$C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02% C, 72.92; H, 4.47; N, 4.89%
15c	210	48	3310, 1635, 1598, 1576, 1540, 1456, 1242	6.86–7.00 (m, 3H), 7.31 (d, J = 8.8 Hz, 1H), 7.50–7.77 (m, 4H), 8.08 (d, J = 8.0 Hz, 1H), 8.40 (d, J = 8.2 Hz, 1H), 9.20 (br s, 1H)	106.9, 115.4, 117.9, 119.4, 121.2, 121.4, 123.2, 124.9, 125.0, 125.2, 125.4, 126.9, 128.5, 135.8, 147.2, 160.3, 168.5	$C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02% C, 72.90; H, 4.51; N, 4.88%
16	118	74	3338, 3058, 1661, 1616, 1590, 1537, 1453, 1348, 1254	6.81–7.87 (m, 2H), 6.96–7.14 (m, 4H), 7.36–7.40 (m, 2H), 7.53–7.58 (m, 2H), 7.42 (d, J = 15.6 Hz, 1H), 9.45 (br s, 1H), 9.84 (br s, 1H)	—	$C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85% C, 75.22; H, 5.21; N, 5.72%

Table 2. Antimicrobial activity of substituted benzamides

Entry	Compound	−log BS	−log SA	−log EC	−log AF	−log AP
1	**3a**	1.30	1.39	1.30	1.69	1.69
2	**3b**	1.15	1.35	1.20	1.55	1.42
3	**7a**	0.93	1.23	1.23	1.53	1.24
4	**7b**	0.96	1.26	1.20	1.56	1.26
5	**7c**	1.04	1.26	1.20	1.56	1.26
6	**7d**	0.96	1.26	1.26	1.56	1.32
7	**7e**	1.00	1.30	1.17	1.60	1.30
8	**7f**	1.00	1.30	1.17	1.60	1.31
9	**7g**	1.38	1.38	1.38	1.69	1.69
10	**7h**	1.27	1.37	1.27	1.58	1.58
11	**7i**	1.26	1.36	1.26	1.36	1.53
12	**8a**	0.93	1.11	1.23	1.43	1.23
13	**8b**	0.96	1.26	1.12	1.45	1.20
14	**8c**	0.96	1.16	1.26	1.56	1.30
15	**8d**	0.96	1.16	1.20	1.56	1.26
16	**8e**	1.10	1.16	1.20	1.60	1.30
17	**8f**	1.00	1.30	1.20	1.60	1.30
18	**8g**	1.38	1.38	1.38	1.58	1.69
19	**8h**	1.07	1.26	1.20	1.67	1.52
20	**8i**	1.41	1.41	1.41	1.71	1.71
21	**9**	1.48	1.48	1.35	1.78	1.83
22	**14a**	1.35	1.35	1.35	1.65	1.65
23	**14b**	1.35	1.23	1.35	1.65	1.65
24	**14c**	1.35	1.23	1.29	1.65	1.35
25	**15a**	1.13	1.26	1.17	1.44	1.30
26	**15b**	1.25	1.32	1.22	1.57	1.62
27	**15c**	1.20	1.25	1.21	1.58	1.62
28	**16**	0.98	1.28	1.16	1.58	1.58
SD[a]		0.17	0.08	0.07	0.09	0.19
S		3.33[b]	3.33[b]	3.33[b]	3.10[c]	3.10[c]

−log BS, −log (1/MIC in μM/mL) *B. subtilis*; −log SA, −log (1/MIC in μM/mL) *S. aureus*; −log EC, −log (1/MIC in μM/mL) *E. coli*; −log AF, −log (1/MIC in μM/mL) *A. ficcum*; −log AP, −log (1/MIC in μM/mL) *A. parasiticus*.

[a] Standard deviation.

[b] Ciprofloxacin.

[c] Salicylic acid.

−log AF more than 1.60, than that of the other synthesized benzamides. Compounds **3a**, **7g**, **7h**, **8g**, **8i**, **14a**, **14b**, **15b**, and **15c** were found to be more active against *A. parasiticus* having −log AP more than 1.58, than the other synthesized benzamides.

Analysis of the results indicates that the presence of OCH_2Ph, COOMe, and OH in compound **9** strongly enhances the activity. Further, a general trend showed that the presence of electron withdrawing groups (NO_2, Cl) leads to increase in the activity in comparison to the presence of electron-releasing group.

In an effort to determine the role of structural features, QSAR studies were undertaken using the linear free energy relationship model (LFER) of Hansch and Fujita.[20] Biological activity data determined as MIC values were first transformed to −log MIC on a molar basis, which was used as a dependent variable in the QSAR study. These were correlated with different molecular descriptors like log of octanol–water partition coefficient (log *P*),[20] molar refractivity (MR),[21] Kier's molecular connectivity ($^2\chi^v$) and shape ($\kappa_1, \kappa\alpha_1$) topological indices,[22] Randic topological index (*R*),[23] Balban topological index (*J*),[24] Wiener topological index (*W*),[25] Total energy (Te),[12] energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO),[26] dipole moment (μ), electronic energy (Ele.E), nuclear energy (Nu.E), and molecular surface area (SA).[27] The values of selected descriptors used in regression analysis are presented in Table 3.

In the present investigation, a set of benzamides consisting of 28 molecules was used for linear regression model generation. The reference drugs were not included in model generation as they belong to a different structural series. A correlation matrix (Table 4) was constructed to find the interrelationship among the parameters, which shows that each parameter selected in the study is highly correlated with the other ($r > 0.7$) except the descriptor log *P*, ionization potential (IP), LUMO, and HOMO. Any combination of these descriptors in multiple regression analysis may result with a model suffering from multi-colinearity.

The correlation of various descriptors with antimicrobial activity is presented in Table 5. From Table 5 it was evident that the topological parameters, valence molecular connectivity indices and shape indices ($^2\chi$, $^2\chi^v$, and $\kappa\alpha_1$), for the benzamides have been found to exhibit best correlation and high statistical significance ($p > 0.01$). The resulting best-fit models applying the principle of Parsimony are reported in Eqs. 1–6 together with statistical parameters of regression. It is important

Table 3. Values of selected descriptors used in the linear regression analysis

Entry	log *P*	MR	$^{0}\chi$	$^{0}\chi^{v}$	$^{1}\chi$	$^{1}\chi^{v}$	$^{2}\chi$	$^{2}\chi^{v}$	IP	LUMO	HOMO
1	4.33	90.39	15.91	12.61	11.33	7.45	9.51	5.09	8.59	−0.24	−8.59
2	3.28	71.44	13.83	10.49	9.08	5.79	8.18	4.18	9.07	−1.63	−9.07
3	2.52	61.01	11.38	8.55	7.75	4.91	6.74	3.37	8.44	−0.42	−8.44
4	2.24	62.70	12.25	8.92	8.16	5.05	7.26	3.52	8.59	−0.42	−8.59
5	2.99	66.05	12.25	9.47	8.15	5.32	7.37	3.87	8.45	−0.25	−8.45
6	2.99	66.05	12.25	9.47	8.15	5.32	7.36	3.87	8.43	−0.30	−8.43
7	3.04	65.81	12.25	9.67	8.15	5.42	7.36	3.98	8.52	−0.71	−8.52
8	3.04	65.81	12.25	9.67	8.16	5.42	7.26	3.92	8.47	−0.47	−8.47
9	2.43	75.66	16.28	10.92	10.36	5.91	9.81	4.25	8.96	−2.13	−8.96
10	3.00	73.14	14.70	10.86	9.47	5.92	8.80	4.36	8.75	−1.64	−8.75
11	2.22	74.79	15.41	11.07	10.02	5.94	8.92	4.11	8.53	−1.05	−8.53
12	2.52	61.01	11.38	8.55	7.77	4.92	6.63	3.34	8.58	−0.23	−8.58
13	2.24	62.70	12.25	8.92	8.18	5.06	7.16	3.49	9.04	−0.50	−9.04
14	2.99	66.05	12.25	9.47	8.16	5.33	7.27	3.84	8.56	−0.19	−8.56
15	2.99	66.05	12.25	9.47	8.16	5.33	7.25	3.84	8.55	−0.24	−8.55
16	3.04	65.81	12.25	9.67	8.18	5.43	7.16	3.89	8.58	−0.38	−8.58
17	3.04	65.81	12.25	9.67	8.16	5.42	7.25	3.95	8.67	−0.52	−8.67
18	3.00	73.14	14.70	10.86	9.49	5.93	8.69	4.33	8.87	−1.55	−8.87
19	2.43	75.66	16.28	10.92	10.38	5.91	9.71	4.22	9.10	−2.04	−9.10
20	4.05	92.08	16.78	12.98	11.74	7.59	10.02	5.24	8.46	−0.19	−8.46
21	3.78	103.61	19.93	15.22	13.60	8.57	11.62	5.92	9.01	−0.60	−9.01
22	3.24	79.15	14.82	11.08	10.16	6.47	9.08	4.65	8.44	−0.68	−8.44
23	3.24	79.15	14.82	11.08	10.16	6.47	9.04	4.65	8.59	−0.60	−8.59
24	3.24	79.15	14.82	11.08	10.15	6.46	9.18	4.68	8.34	−0.76	−8.34
25	2.24	62.70	12.25	8.92	8.16	5.05	7.26	3.52	8.60	−0.42	−8.60
26	3.53	77.46	13.95	10.71	9.75	6.33	8.56	4.50	8.62	−0.76	−8.62
27	3.53	77.46	13.95	10.71	9.75	6.33	8.53	4.50	8.70	−0.66	−8.70
28	2.93	71.25	12.79	9.71	8.74	5.57	7.55	3.78	8.44	−0.34	−8.44

Table 4. Correlation matrix for log BS with molecular descriptors

	log BS	log *P*	MR	$^{0}\chi$	$^{0}\chi^{v}$	$^{1}\chi$	$^{1}\chi^{v}$	$^{2}\chi$	$^{2}\chi^{v}$	κ_1	κ_2	$\kappa\alpha_1$	$\kappa\alpha_2$	IP	LUMO	HOMO
log BS	1.000															
log *P*	0.433	1.000														
MR	0.848	0.719	1.000													
$^{0}\chi$	0.905	0.455	0.929	1.000												
$^{0}\chi^{v}$	0.841	0.676	0.984	0.951	1.000											
$^{1}\chi$	0.899	0.581	0.980	0.978	0.976	1.000										
$^{1}\chi^{v}$	0.823	0.763	0.994	0.899	0.980	0.962	1.000									
$^{2}\chi$	0.934	0.486	0.934	0.993	0.945	0.978	0.905	1.000								
$^{2}\chi^{v}$	0.841	0.778	0.976	0.894	0.974	0.942	0.985	0.910	1.000							
κ_1	0.870	0.420	0.909	0.994	0.940	0.963	0.875	0.977	0.863	1.000						
κ_2	0.763	0.522	0.924	0.933	0.937	0.942	0.899	0.902	0.848	0.952	1.000					
$\kappa\alpha_1$	0.850	0.422	0.898	0.987	0.942	0.949	0.868	0.964	0.861	0.996	0.949	1.000				
$\kappa\alpha_2$	0.729	0.542	0.913	0.915	0.938	0.922	0.895	0.878	0.849	0.938	0.994	0.944	1.000			
IP	0.278	−0.137	0.196	0.413	0.270	0.305	0.163	0.372	0.171	0.443	0.342	0.453	0.337	1.000		
LUMO	−0.444	0.229	−0.138	−0.431	−0.214	−0.272	−0.079	−0.437	−0.151	−0.443	−0.226	−0.448	−0.206	−0.667	1.000	
HOMO	−0.278	0.137	−0.196	−0.413	−0.270	−0.305	−0.163	−0.372	−0.171	−0.443	−0.342	−0.453	−0.337	−1.000	0.667	1.000

to note that all these models were developed by using the entire set ($n = 28$), since no outliers were identified.

The quality of the models is indicated by the following parameters: r, correlation coefficient; F, Fisher's statistics; and s, standard error of estimation, r^2_{cv}, cross-validated r^2 obtained by 'leave one out' (LOO) method.

QSAR model for antibacterial activity against *B. subtilis*

$$-\log \mathrm{BS} = 0.137\,{}^{2}\chi + 0.019 \quad (1)$$

$n = 28$, $r = 0.934$, $F = 178.89$, $s = 0.064$, $r^2_{cv} = 0.837$.

QSAR model for antibacterial activity against *S. aureus*

$$-\log \mathrm{SA} = 0.065\kappa\alpha_1 + 0.920 \quad (2)$$

$n = 28$, $r = 0.810$, $F = 49.82$, $s = 0.051$, $r^2_{cv} = 0.608$.

QSAR model for antibacterial activity against *E. coli*

$$-\log \mathrm{EC} = 0.049\,{}^{2}\chi + 0.840 \quad (3)$$

$n = 28$, $r = 0.784$, $F = 41.72$, $s = 0.048$, $r^2_{cv} = 0.529$.

$$-\log \mathrm{EC} = 0.054\,{}^{2}\chi - 0.075\mathrm{IP} + 1.446 \quad (4)$$

$n = 28$, $r = 0.785$, $F = 23.65$, $s = 0.047$, $r^2_{cv} = 0.534$.

Table 5. Correlation of molecular descriptors with antimicrobial activity of substituted benzamides

	−log BS	−log SA	−log EC	−log AN	−log AP
log *P*	0.433	0.348	0.340	0.695	0.513
MR	0.848	0.713	0.696	0.696	0.867
$^{0}\chi$	0.905	0.786	0.761	0.612	0.885
$^{0}\chi^{v}$	0.841	0.751	0.681	0.693	0.844
$^{1}\chi$	0.899	0.754	0.748	0.643	0.890
$^{1}\chi^{v}$	0.823	0.689	0.663	0.710	0.829
$^{2}\chi$	0.934	0.769	0.785	0.644	0.899
$^{2}\chi^{v}$	0.841	0.676	0.671	0.757	0.822
κ_1	0.870	0.803	0.741	0.590	0.869
κ_2	0.763	0.784	0.663	0.588	0.825
$\kappa\alpha_1$	0.850	0.811	0.713	0.597	0.848
$\kappa\alpha_2$	0.729	0.787	0.620	0.600	0.793
R	0.899	0.754	0.748	0.643	0.890
B	−0.362	−0.088	−0.281	−0.472	−0.379
W	0.831	0.760	0.712	0.654	0.839
Te	−0.860	−0.791	−0.708	−0.524	−0.821
Ele.E	−0.884	−0.783	−0.743	−0.600	−0.860
Nu.E	0.879	0.775	0.741	0.605	0.858
SA	0.821	0.737	0.698	0.663	0.839
IP	0.278	0.367	0.110	0.101	0.311
LUMO	−0.444	−0.429	−0.307	−0.121	−0.414
HOMO	−0.278	−0.367	−0.110	−0.101	−0.311

Table 6. Observed and predicted antimicrobial activity of substituted benzamides using the best QSAR models

Entry	−log BS using Eq. 1			−log SA using Eq. 2			−log EC using Eq. 4			−log AF using Eq. 5			−log AP using Eq. 6		
	Obs.	Pred.	Res.	Obs.	Pred.	Res.	Obs.	Pred.	Res.	Obs.	Pred.	Res.	Obs.	Pred.	Res.
1	1.30	1.32	−0.02	1.39	1.36	0.03	1.30	1.32	−0.02	1.69	1.69	0.00	1.69	1.70	−0.01
2	1.15	1.14	0.01	1.35	1.30	0.05	1.20	1.21	−0.01	1.55	1.58	−0.03	1.42	1.43	−0.01
3	0.93	0.94	−0.01	1.23	1.20	0.03	1.23	1.18	0.05	1.53	1.49	0.04	1.24	1.27	−0.03
4	0.96	1.01	−0.05	1.26	1.23	0.03	1.20	1.20	0.00	1.56	1.51	0.05	1.26	1.32	−0.06
5	1.04	1.03	0.01	1.26	1.24	0.02	1.20	1.22	−0.02	1.56	1.55	0.01	1.26	1.32	−0.06
6	0.96	1.03	−0.07	1.26	1.24	0.02	1.26	1.22	0.04	1.56	1.55	0.01	1.32	1.32	0.00
7	1.00	1.03	−0.03	1.30	1.25	0.05	1.17	1.21	−0.04	1.60	1.56	0.04	1.30	1.32	−0.02
8	1.00	1.01	−0.01	1.30	1.25	0.05	1.17	1.21	−0.04	1.60	1.55	0.05	1.31	1.32	−0.01
9	1.38	1.36	0.02	1.38	1.37	0.01	1.38	1.31	0.07	1.69	1.59	0.10	1.69	1.59	0.10
10	1.27	1.22	0.05	1.37	1.33	0.04	1.27	1.27	0.00	1.58	1.61	−0.03	1.58	1.48	0.10
11	1.26	1.24	0.02	1.36	1.35	0.01	1.26	1.29	−0.03	1.36	1.58	−0.22	1.53	1.55	−0.02
12	0.93	0.93	0.00	1.11	1.20	−0.09	1.23	1.17	0.06	1.43	1.49	−0.06	1.23	1.27	−0.04
13	0.96	1.00	−0.04	1.26	1.23	0.03	1.12	1.16	−0.04	1.45	1.50	−0.05	1.20	1.32	−0.12
14	0.96	1.01	−0.05	1.16	1.24	−0.08	1.26	1.20	0.06	1.56	1.55	0.01	1.30	1.32	−0.02
15	0.96	1.01	−0.05	1.16	1.24	−0.08	1.20	1.20	0.00	1.56	1.54	0.02	1.26	1.32	−0.06
16	1.10	1.01	0.09	1.16	1.25	−0.09	1.20	1.19	0.01	1.60	1.56	0.04	1.30	1.32	−0.02
17	1.00	1.00	0.00	1.30	1.25	0.05	1.20	1.19	0.01	1.60	1.55	0.05	1.30	1.32	−0.02
18	1.38	1.35	0.03	1.38	1.37	0.01	1.38	1.29	0.09	1.58	1.59	−0.01	1.69	1.59	0.10
19	1.07	1.21	−0.14	1.26	1.33	−0.07	1.20	1.26	−0.06	1.67	1.60	0.07	1.52	1.48	0.04
20	1.41	1.39	0.02	1.41	1.39	0.02	1.41	1.36	0.05	1.71	1.71	0.00	1.71	1.75	−0.04
21	1.48	1.61	−0.13	1.48	1.51	−0.03	1.35	1.40	−0.05	1.78	1.78	0.00	1.83	1.98	−0.15
22	1.35	1.26	0.09	1.35	1.30	0.05	1.35	1.31	0.04	1.65	1.64	0.01	1.65	1.56	0.09
23	1.35	1.26	0.09	1.23	1.30	−0.07	1.35	1.30	0.05	1.65	1.64	0.01	1.65	1.56	0.09
24	1.35	1.28	0.07	1.23	1.30	−0.07	1.29	1.32	−0.03	1.65	1.64	0.01	1.35	1.56	−0.21
25	1.13	1.01	0.12	1.26	1.23	0.03	1.17	1.20	−0.03	1.44	1.51	−0.07	1.30	1.32	−0.02
26	1.25	1.19	0.06	1.32	1.27	0.05	1.22	1.27	−0.05	1.57	1.62	−0.05	1.62	1.51	0.11
27	1.20	1.19	0.01	1.25	1.27	−0.02	1.21	1.26	−0.05	1.58	1.62	−0.04	1.62	1.51	0.11
28	0.98	1.05	−0.07	1.28	1.26	0.02	1.16	1.23	−0.07	1.58	1.54	0.04	1.58	1.39	0.19

QSAR model for antifungal activity against *A. ficcum*

$$-\log \mathrm{AF} = 0.114\,{}^{2}\chi^{v} + 1.104 \quad (5)$$

$n = 28$, $r = 0.757$, $F = 34.93$, $s = 0.060$, $r^2_{cv} = 0.529$.

QSAR model for antifungal activity against *A. parasiticus*

$$-\log \mathrm{AP} = 0.121\,{}^{1}\chi + 0.330 \quad (6)$$

$n = 28$, $r = 0.899$, $F = 98.63$, $s = 0.089$, $r^2_{cv} = 0.733$.

The coefficient of $^2\chi$ in the mono-parametric model in Eq. 1 is positive indicating thereby that antibacterial activity of benzamides against *B. subtilis* is directly proportional to the magnitude of $^2\chi$. The antibacterial activity increases with an increase in magnitude of $^2\chi$. This is evidenced by the values of $^2\chi$ in Table 3. The values of $^2\chi$ for compounds **8i** (entry 20) and **9** (entry 21) are 10.02 and 11.62, respectively, which are higher than the $^2\chi$ values of other compounds which make them the most active compounds against *B. subtilis* with $-\log$ BS of 1.41 and 1.48 (Table 2), respectively. Similarly the compounds **7a** (entry 3) and **8a** (entry 12) having the minimum $^2\chi$ values of 6.74 and 6.63, respectively, have minimum activity. Similar trend was observed in case of *S. aureus, E. coli, A. ficcum*, and *A. parasiticus* with $\kappa\alpha_1$, $^2\chi$, $^2\chi^v$, and $^2\chi$, respectively.

In order to confirm our results we have predicted the activities of benzamide derivatives using the model expressed by Eqs. 1–6 [except (3)] and compared them with the observed values. The data presented in Table 6 show that the observed and the estimated activities are very close to each other evidenced by low values of residual activity.

The cross-validation of the models was also done by leave one out (LOO) technique.[28] The high cross-validated correlation coefficient (r^2_{cv} or q^2) values obtained for the best QSAR models indicated their reliability in predicting the antimicrobial activity of substituted benzamides. But one should not forget the recommendations of Golbraikh et al.,[29] who have recently reported that the only way to estimate the true predictive power of a model is to test their ability to predict accurately the biological activities of compounds. The low residual activity values observed justify the selection of the linear regression models expressed by Eqs. 1–6. Further the plot of linear regression predicted $-\log$ BS values against the observed $-\log$ BS values also favors the model expressed by Eq. 1 (Fig. 3).

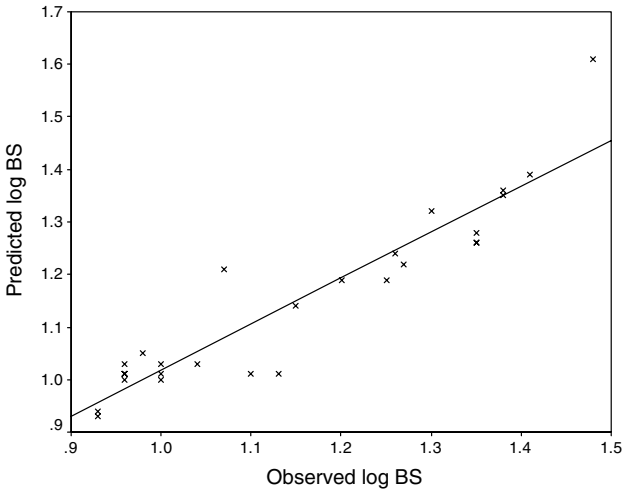


Figure 3. Plot of predicted log BS activity values against the experimental log BS values for the linear regression developed model by Eq. 1.

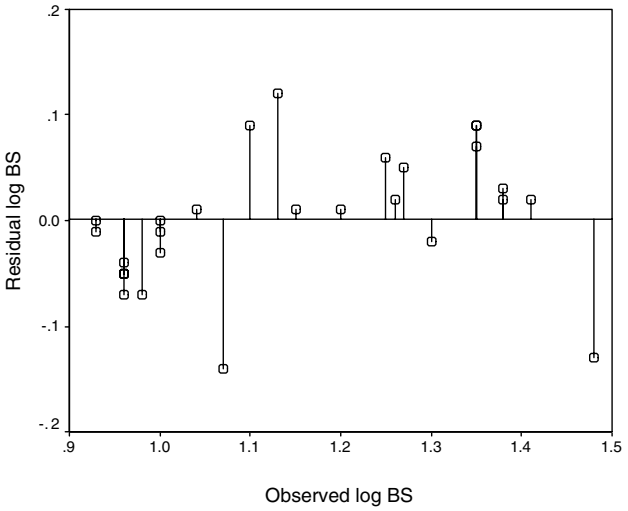


Figure 4. Plot of residual log BS activity values against the experimental log BS values.

To investigate the existence of a systemic error in developing the QSAR model, the residuals of linear regression predicted values of $-\log$ BS were plotted against the observed $-\log$ BS values in Figure 4. The propagation of the residuals on both sides of zero indicates that no systemic error exists in the development of linear regression model.[30]

Even though the sample size and the 'Rule of Thumb' allowed us to go for development of multi-parametric model in multiple linear regression analysis, the high interrelationship among the parameters restricted us for mono-parametric model. The other statistically significant models derived are presented in Table 7. The multi-colinearity occurs when two independent variables are correlated with each other that becomes a problem for a theoretical statistician. One should note that the change in signs of the coefficients, a change in the values of previous coefficient, change of significant variable into insignificant one or an increase in standard error of the estimate on addition of an additional parameter to the model are indications of high interrelationship among descriptors.

2. Conclusions

From the results and discussion made above we conclude that the benzamides are effective against the microbial species tested. The results obtained from present investigation of in vitro antimicrobial activity studies indicate that the *N*-(2-hydroxyphenyl)-3-methoxy-2-nitrobenzamide (**8i**, entry 20) and *N*-(2-hydroxy-6-carbmethoxyphenyl)-2-benzyloxybenzamide (**9**, entry 21) are the most effective ones. Further, a general trend showed that the presence of electron-withdrawing groups (NO_2, Cl) leads to increase in the activity in comparison to the presence of electron releasing group. The topological parameters especially, the valence molecular connectivity indices and shape indices ($^2\chi$, $^2\chi^v$, and $\kappa\alpha_1$) can be used successfully for modeling antimicrobial activity of

Table 7. Regression analysis and quality of correlation for modeling antimicrobial activity of benzamides ($r^2_{CV} > 0.5$)

S.No.	QSAR Model	*n*	*r*	r^2_{CV}	*F*	*s*
B. subtilis (−log BS =)						
1	0.015 MR + 0.066	28	0.848	0.656	66.59	0.096
2	0.080 $^0\chi$ + 0.041	28	0.905	0.757	117.95	0.077
3	0.103 $^0\chi^v$ + 0.076	28	0.841	0.608	62.95	0.098
4	0.114 $^1\chi$ + 0.089	28	0.899	0.738	109.60	0.080
5	0.169 $^1\chi^v$ + 0.149	28	0.822	0.611	54.49	0.103
6	0.252 $^2\chi^v$ + 0.091	28	0.840	0.659	62.78	0.098
7	0.065 κ_1 + 0.159	28	0.870	0.689	81.32	0.089
8	0.106 κ_2 + 0.388	28	0.762	0.503	36.16	0.118
9	0.074 $\kappa\alpha_1$ + 0.180	28	0.850	0.645	67.72	0.095
10	0.0004 *W* + 0.821	28	0.831	0.485	57.90	0.107
11	−0.0003 Te + 0.247	28	0.860	0.704	74.04	0.093
12	0.141 $^2\chi$ − 0.067 IP + 0.559	28	0.937	0.820	90.58	0.064
S. aureus (−log SA =)						
13	0.033 $^0\chi$ + 0.828	28	0.786	0.569	42.06	0.054
14	0.044 $^0\chi^v$ + 0.829	28	0.751	0.510	33.72	0.057
15	0.046 $^1\chi$ + 0.862	28	0.754	0.516	34.27	0.057
16	0.054 $^2\chi$ + 0.843	28	0.768	0.536	37.58	0.055
17	0.029 κ_1 + 0.851	28	0.802	0.597	47.09	0.052
18	0.052 κ_2 + 0.914	28	0.784	0.562	41.53	0.054
19	0.065 $\kappa\alpha_2$ + 0.920	28	0.787	0.559	42.38	0.053
20	−0.0001 Te + 0.891	28	0.791	0.577	43.57	0.053
E. coli (−log EC =)						
21	0.054 $^2\chi$ − 0.075 IP + 1.446	28	0.785	0.534	23.65	0.047
A. ficcum (−log AF =)						
22	0.074 $^1\chi^v$ + 1.149	28	0.710	0.455	26.43	0.064
A. parasiticus (−log AP =)						
23	0.016 MR + 0.266	28	0.867	0.698	78.92	0.097
24	0.084 $^0\chi$ + 0.293	28	0.884	0.732	93.91	0.091
25	0.111 $^0\chi^v$ + 0.299	28	0.844	0.629	64.65	0.105
26	0.184 $^1\chi^v$ + 0.374	28	0.829	0.632	57.08	0.109
27	0.141 $^2\chi$ + 0.289	28	0.807	0.774	109.62	0.085
28	0.266 $^2\chi^v$ + 0.345	28	0.822	0.633	54.29	0.111
29	0.069 κ_1 + 0.394	28	0.869	0.698	80.21	0.097
30	0.123 κ_2 + 0.573	28	0.825	0.600	55.45	0.110
31	0.079 $\kappa\alpha_1$ + 0.419	28	0.848	0.653	66.34	0.103
32	0.147 $\kappa\alpha_2$ + 0.624	28	0.792	0.539	43.97	0.119
33	0.0004 *W* + 1.102	28	0.838	0.520	61.70	0.106
34	−0.0002 Te + 0.532	28	0.820	0.638	53.68	0.111

benzamides against the microbial species included in the present study. Contribution of topological descriptors in describing the antimicrobial activity of benzamides was further evidenced by the results of our previous studies.[12,13,15] The low residual activity and high cross-validated r^2values (r^2_{cv}) observed indicated the predictive ability of the developed QSAR models.

3. Experimental

Melting points were determined in open capillaries and are uncorrected. Carbonyldiimidazole (CDI) was purchased from Aldrich and used without further purification. THF was distilled from sodium/benzophenone prior to use. FTIR spectra were obtained in KBr on Perkin-Elmer Spectrum RX1 instruments and are reported in cm^{-1}. Unless otherwise noted ^1H and ^{13}C NMR spectra were determined on Bruker Avance II 400 and 100 MHz NMR Spectrometer, respectively, in $CDCl_3$–DMSO-d_6 and are expressed as ppm with respect to TMS. Elemental analysis was carried out on Perkin-Elmer 2400 instrument.

All the synthesized benzamides are new compounds except **7a** (no data were reported),[31] **8d**,[32] and **9**.[17]

3.1. General procedure

Carbonyldiimidazole (CDI) (4.86 g, 30 mmol) was dissolved in 30 mL dry THF with stirring at room temperature under nitrogen atmosphere and appropriate benzoic acid/naphthoic acid/cinnamic acid (30 mmol) was added carefully. The reaction mixture was further stirred for 10 min and then after the evolution of CO_2 ceased, substituted aniline (20 mmol) was added. The stirring was continued for additional 10 min at room temperature and then refluxed for 12–18 h. After com-

pletion of the reaction, monitored by TLC, reaction mixture was concentrated to obtain crude product. The crude product was purified by column chromatography using either hexane or 10–20% EtOAc in hexane.

3.2. Biological studies

Using serial dilution technique in double strength nutrient broth-I.P. and Sabouraud dextrose broth-I.P. as a medium, the in vitro antibacterial and antifungal activity studies of the synthesized compounds against *S. aureus*, *B. subtilis*, *E. coli*, *A. ficcum*, and *A. parasiticus* were carried out. The benzamides were dissolved in DMSO to give a concentration of 10 μg/mL (stock solution).

3.2.1. Antibacterial assay. Twenty-four-hour fresh cultures were obtained by inoculation of respective bacteria in double strength nutrient broth-I.P. followed by incubation at 37 ± 1 °C. The stock solution of synthesized benzamides was serially diluted in tube containing 1 mL of sterile double strength nutrient broth-I.P. to get a concentration of 5–0.156 μg/mL and then inoculated with 100 μL of suspension of respective organisms in sterile saline (*S. aureus*, *B. subtilis*, and *E. coli*). The inoculated tubes were incubated at 37 ± 1 °C for 24 h and minimum inhibitory concentrations (MIC) were determined. From the observed MIC values, the exact MIC values were determined by making suitable solution of stock solution.

3.2.2. Antifungal assay. The antifungal activity of synthesized substituted benzamides against the fungal species *A. ficcum* and *A. parasiticus* was determined by serial dilution method similar to *antibacterial assay* using Sabouraud dextrose broth-I.P. following the incubation condition of 25 ± 1 °C for a period of 7 days.

3.3. QSAR analysis

The calculations of molecular descriptors of benzamides as well as the regression analysis were carried out by using the molecular package TSAR 3D version 3.3.[33] The details of calculation of these descriptors are available in the literature[20–27] and therefore, they are not mentioned here.

3.4. Cross-validation

The models were cross-validated by 'leave one out' scheme[34] where a model is built with N-1 compounds and the *N*th compound is predicted. Each compound is left out of the model derivation and predicted in turn. An indication of the performance of the model is obtained from the cross-validated (or predictive q^2) method which is defined as

$$q^2 = (\mathrm{SD} - \mathrm{PRESS}/\mathrm{SD})$$

where SD is the sum of squares deviation for each activity from the mean. PRESS (or predictive sum-of-squares) is the sum of the squared difference between the actual and that of the predicted values when the compound is omitted from the fitting process. The model with high q^2 value is said to have high predictability.

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