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Synthesis and antimicrobial activity of novel 4-(1*H*-benzo[*d*]imidazol-2-yl)-4,5-dihydro-benzo[*f*][1,4]-oxazepin-3(2*H*) ones

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A novel series of 4-(1*H*-benzo[*d*]imidazol-2-yl)-4,5-dihydro-benzo[*f*][1,4]-oxazepin-3(2*H*)-ones (**4**) have been synthesized by a simple reaction sequence. The reaction of 2-amino benzimidazole (**1**) with salicylaldehydes, followed by reduction with $NaBH_4$, and *in situ* chloroacetylation and cyclization with chloroacetyl chloride and triethyl amine affords the title compounds. The structures of the newly synthesized compounds (**2-4**) have been characterized by IR, ^1H and ^{13}C NMR and mass spectral data. The title compounds (**4**) have been screened for their *in vitro* antimicrobial activity against bacterial and fungal strains by broth dilution method and agar cup bioassay methods, respectively. Some of the compounds exhibit good antimicrobial activity, when compared to the standard drugs.

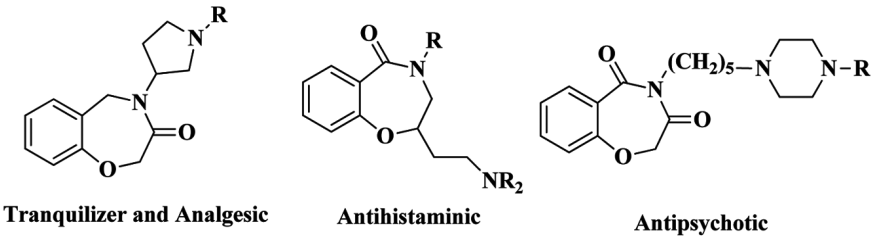
Keywords: Benzimidazolyl benzo[*f*][1,4]oxazepines, *In situ* cyclization, Simple synthetic sequence, Antimicrobial activity, Minimum inhibitory concentration

The development of drug resistance towards the clinically used antimicrobial agents has increased the demand for the design and synthesis of new chemical entity that possess promising antimicrobial activity[1,2]. Moreover, in some cases, the use of antimicrobial drugs to treat infectious diseases causes side effects[3,4]. There is an urgent need for discovery of new and more effective antimicrobial agents with minimal or no side effects. Benzo-1,4-oxazepines have been attracting much interest due to the wide range of biological activities. Among these, antiepileptic[5], anticonvulsant[6], anti-inflammatory[7], antihistaminic[8], tranquilizer and analgesic[9], and antipsychotic[10] activities are worth mentioning. Considering the structural characteristics of the benzoxazepin-3-ones, the existence of seven membered heterocyclic ring system with -N-C=O group, similar to protein amide bond, it is reasonable to expect inherent physiological activities. Benzimidazole is an important nucleus that has been extensively used in medicinal chemistry. They are known to exhibit anti-inflammatory[11], antibiotic[12], antihelminthic[13], anticancer[14], and antiviral[15] activity. Molecular hybridization involving the fusion of two or more pharmacophoric submits with potential bioactivity can lead to compounds having improved affinity and effective than the parent compounds with reduced side effects, while retaining the desired characteristics of original template. Various literature reports have explored this methodology in designing newer analogues as potential candidates in biological evaluation[16-18].

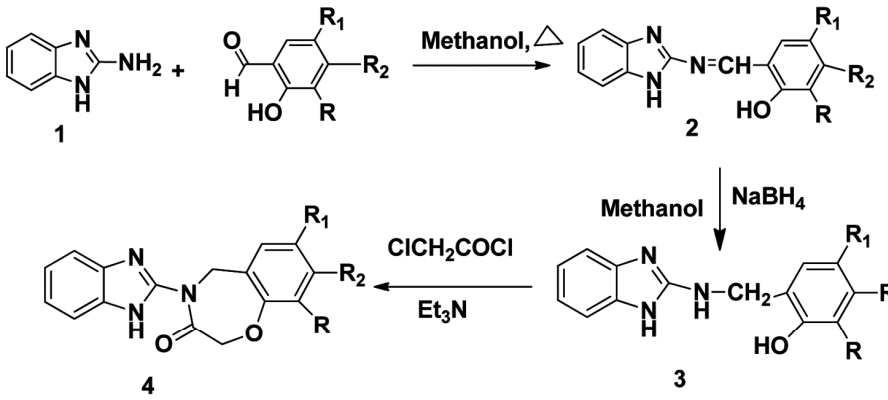
Based on these findings, we are interested to construct benzimidazole-benzoxazepine (Scheme 1) hybrids by utilizing a simple methodology to evaluate the antimicrobial activity of the compounds. We herein, report the synthesis and antimicrobial activity of novel 4-(1*H*-benzo[*d*]imidazol-2-yl)-4,5-dihydro-benzo[*f*][1,4]-oxazepin-3(2*H*)-ones.

Results and Discussion

The reaction sequence for the title compounds is outlined in Scheme 2. The 2- amino benzimidazole **1** on condensation with different substituted salicyladehydes in refluxing methanol afforded the corresponding 2-(1*H*-benzo[*d*] imidazol-2-ylimino) methyl phenols **2**, which on reduction with sodium borohydride produced 2-(1*H*-benzo[*d*] imidazol-2-ylamino) methyl phenols **3**. The compounds **3** on treatment with chloroacetyl chloride in presence of triethyl amine underwent chloroacetylation followed by cyclization *in situ* to furnish 4-(1*H*-benzo[*d*]imidazol-2-yl)-4,5-dihydro-benzo[*f*][1,4]-oxazepin-3(2*H*)-ones **4** in good yields.



Scheme 1 — Biologically active benzo-1,4-oxazepinones



2, 3 & 4

	R	R^1	R^2		R	R^1	R^2
a,	H	H	H	**e,**	Br	H	H
b,	OCH_3	H	H	**f,**	Br	Br	H
c,	Cl	H	H	**g,**	OCH_3	Br	H
d,	Cl	Cl	H	**h,**	H	H	CH_3

Scheme 2 — Reaction sequence for the title compounds

The structures of all the newly synthesized compounds were established on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. IR spectrum of compound **2a** exhibited strong absorption bands around 1650, 3320 and 3400 cm^{-1} due to –C=N–, NH and OH functional groups stretching vibrations respectively. ^{1}H NMR spectrum of **2a** displayed a characteristic peak at δ 8.90 assignable to azomethine proton. ^{13}C NMR and mass spectral data is in agreement with the Schiff's base **2a**. IR spectrum of **3a** showed absorption bands at 3380, 3392 and 3260 cm^{-1} due to 2 NH and OH functional groups, respectively. ^{1}H NMR spectra of **3a** displayed NH proton signal at δ 6.34 which is D_2O exchangeable, and CH_2 protons signal appeared as a singlet at δ 4.20 confirming the reduction. ^{13}C NMR and mass spectral data is in agreement with the proposed structure. ^{1}H NMR spectra of compound **4a** displayed two distinct singlets at δ 4.90 and 5.30 due to newly formed 1,4-oxazepine ring NCH_2 and OCH_2 protons, respectively. ^{13}C NMR spectra of **4a** exhibited NCH_2 and OCH_2 carbon signals at δ 47.88 and 71.82, respectively. The mass spectra of **4a** is in agreement with the cyclized structure, which showed the molecular ion $[M+H]^+$ peak at *m/z* 280.

Antibacterial activity

All the title compounds **4a-h** were screened for their *in vitro* antimicrobial activity (Table 1) against Gram-positive bacterial strains *Bacillus subtilis (Bs)* (MTCC 441), *Bacillus sphaericus (Bsp)* (MTCC 511), *Staphylococcus aureus (Sa)* (MTCC 96), and Gram-negative bacteria *viz*., *Pseudomonas aeruginosa (Pa)* (MTCC 741), *Klebsiella aerogenes* (*Ka*) (MTCC 39), and *Chromobacterium violaceum (Cv)* (MTCC 2656) at 100 µg/ml concentration. The *in vitro* antibacterial activity of the tested compounds was assessed by minimum inhibitory concentration (MIC) using broth

Table 1 — Antimicrobial activity of 4- (1*H*-benzo[*d*]imidazol-2-yl)-4,5-dihydrobenzo[*f*][1,4]-oxazepin-3(2*H*)-ones (**4a-h)**

Compd	Minimum Inhibitory Concentration (MIC)[a,b] Zone of inhibition mm [a,b]											
	Bacterial strains						Fungal Strains					
	BS	*Bsp*	*Sa*	*Pa*	*Ka*	*Cv*	Fo	*Vd*	*As*	*Rs*	*Cc*	*Pap*
4a	18	20	22	23	18	20	11	12	11	10	12	10
4b	10	11	8	9	9	11	9	7	10	8	8	11
4c	16	13	15	15	14	10	13	12	15	13	12	14
4d	15	17	20	15	16	17	14	13	16	13	14	15
4e	17	14	15	15	13	16	12	15	10	11	12	16
4f	12	16	16	11	14	15	13	14	15	14	11	14
4g	11	12	10	13	12	9	11	10	12	11	10	11
4h	8	9	9	7	8	9	8	7	9	6	7	10
Ciprofloxacin	20	22	26	25	20	22	–	–	–	–	–	–
Fiuconazole	–	–	–	–	–	–	16	16	20	16	18	22

[a]Negative control (acetone) – no activity.
[b]Concentration 100 µg/mL

dilution method [19]. *Ciprofloxacin* was used as standard drug for comparison. All the compounds showed moderate to good activity against the bacterial strains used in the present investigation. The compounds **4b, 4g** and **4h** are highly active, because the activity is considerably affected by the presence of methoxy and methyl substitutes on benzene ring, besides the presence of the basic skeleton benzimidazolyl-1,4-benzoxazepine ring. Compounds **4c, 4d, 4e,** and **4f** carrying chloro and bromo substituents on the benzene ring exhibited moderate activity. Compound **4a** showed least activity. However, the degree of inhibition varied both with the test compound as well as with the Gram-negative and Gram-positive bacteria used in the present investigation.

Antifungal activity

The antifungal activity of compounds **4a-h** was evaluated against six fungal strains *i.e. Fusarium oxysporum (Fo)*, *Verticillium dahlia (Vd)*, *Alternaria solani (As)*, *Rhizoctonia solani (Rs)*, *Colletotrichum capsici (Cc),* and *Pythium aphanidermatum (Pap)* at 100 µg/ml concentration. The *in vitro* antifungal activity of the compounds was assessed by minimum inhibitory concentration (MIC) using agar cup bioassay method[20]. *Flucanazole* was used as the standard drug for comparison.

All the compounds showed good activity against the tested fungal strains. Among all, compounds **4b**, **4g** and **4h** exhibited high toxicity by inhibiting the growth of fungi to a remarkable extent, when compared to standard drug *Flucanazole*. This may be due to the presence of methoxy and methyl substituents on benzene ring, besides the presence of basic skeleton benzimidazolyl-1,4-benzoxazapine ring. Surprisingly, compound **4a** showed good activity. Compounds **4c, 4d, 4e** and **4f** are moderately active. Moreover, the degree of spore germination inhibition varied with the test compound as well as with the fungi under investigation.

Experimental Section

Melting points have been determined on a Cintex melting point apparatus. TLC has been performed on Merck precoated 60 F_{254} silica gel plates. Visualization is done by exposing to iodine vapour. IR spectra (KBr pellet) have been recorded on a Perkin- Elmer BX series FT-IR spectrometer. ^{1}H NMR spectra are recorded on a Bruker 300 MHz spectrometer. ^{13}C NMR spectra are recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in δ ppm with tetramethyl silane as an internal standard. ESI -MS spectra are recorded on an Agilent LC-MSD mass spectrometer. Elemental analyses are performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

General procedure for the synthesis of 2-(((1*H*-benzo[*d*]imidazol-2-yl)imino)methyl)phenols, 2a-h

A solution of 2-amino benzimidazole **(1)** (0.001 mmol) and different salicylaldehydes (0.01 mmol) in methanol (10 mL) were refluxed for 4-6 h. Reaction progress was monitored by TLC (30% ethyl acetate in n-hexane). The reaction mixture was cooled, the Schiff's base that separated was filtered, washed with cold methanol, and dried under vacuum. Recrystallization was effected from methanol.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)imino)methyl)-phenol, 2a: Pale Yellow solid. Yield 80%. m.p. 140-42°C. IR (KBr): 3400 (OH), 3320 (NH), 1650 cm^{-1} cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96-7.09 (m, 8H, Ar-H), 8.90 (s, 1H, –CH=N–), 10.13 (s, 1H, NH, D_2O exchangeable), 12.44 (s, 1H, Ar-OH, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 115.32, 115.45, 117.59, 118.45, 119.49, 123.02, 123.11, 133.35, 134.66, 138.91,138.99, 157.45, 161.60, 166.87; ESI-MS: *m/z* 238 $[M + H]^+$. Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.88; H, 4.64; N, 17.72. Found: C, 70.89; H, 4.67; N, 17.73%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)imino)methyl)-6-methoxyphenol 2b: Pale Yellow solid. Yield 82%. m.p. 148-150°C. IR (KBr): 33448 (OH),3328 (NH), 1658 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3) 7.13-7.69 (m, 7H, Ar-H), 8.86 (s, 1H, –CH=N–), 10.12 (s,1H, NH, D_2O exchangeable), 12.42 (s, 1H, Ar-OH, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 56.42, 115.34, 115.48, 117.62, 118.48, 119.52, 123.07, 123.16, 133.38, 134.69, 138.96,138.99, 157.48, 161.63, 165.02; ESI-MS: *m/z* 268 $[M + H]^+$. Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.86; N, 15.73. Found: C, 67.45; H, 4.90; N, 15.76%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)imino)methyl)-6-chlorophenol, 2c: Pale Yellow solid. Yield 78%. m.p. 155-56°C. IR (KBr): 3406 (OH), 3326 (NH), 1659 cm^{-1} (C=N); ^{1}H NMR(300 MHz, $CDCl_3$): δ 6.96-7.09 (m, 7H, Ar-H), 8.96 (s, 1H, –CH=N–), 10.15 (s,1H, NH, D_2O exchangeable), 12.46 (s, 1H, Ar-OH, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 115.35, 115.48, 117.61, 118.47, 119.52, 123.07, 123.15, 133.38, 134.68, 138.96,138.99, 157.48, 161.64, 164.29; ESI-MS: *m/z* 272 $[M + H]^+$. Anal. Calcd for $C_{14}H_{10}ClN_3O$: C, 61.99; H, 3.69; N, 15.49. Found: C, 61.96; H, 3.71; N, 15.45%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)imino)methyl)-4,6-dichlorophenol, 2d: Pale Yellow solid; Yield 75%; m.p. 159-61°C. IR (KBr): 3410 (OH), 3330 (NH), 1665 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13-7.77 (m, 6H, Ar-H), 9.03 (s, 1H, –CH=N–), 10.17 (s,1H, NH, D_2O exchangeable), 12.49 (s, 1H, Ar-OH, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 115.37, 115.51, 117.64, 118.51, 119.56, 123.09, 123.18, 133.41, 134.70, 138.93,138.99, 157.52, 161.68, 165.31; ESI-MS: *m/z* 306 $[M+ H]^+$. Anal. Calcd for $C_{14}H_9Cl_2N_3O$: C, 55.08; H, 2.95; N, 13.77. Found: C, 55.11; H, 2.96; N, 13.74%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)imino)methyl)-6-bromophenol, 2e: Brown solid. Yield 70%. m.p. 162-64°C. IR (KBr): 3432 (OH), 3320 (NH), 1661 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17-7.80 (m, 7H, Ar-H), 8.98 (s, 1H, –CH=N–), 10.18 (s,1H, NH, D_2O exchangeable), 12.49 (s, 1H, Ar-OH, D_2O exchangeable); ^{13}C NMR(75MHz, $CDCl_3$): δ 115.39, 115.50, 117.65, 118.49, 119.55, 123.10, 123.18, 133.40, 134.70, 138.96,138.99, 157.51, 161.66, 166.27; ESI-MS: *m/z*, 316 $[M+ H]^+$; Anal. Calcd for $C_{14}H_{10}BrN_3O$: C, 53.33; H, 3.17; N, 13.33. Found: C, 53.30; H, 3.20; N, 13.31.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)imino)methyl)-4,6-dibromophenol, 2f: Brown solid. Yield 70%. m.p. 166-68°C. IR (KBr): 3434 (OH), 3325 (NH), 1663 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17-7.87 (m, 6H, Ar-H), 9.02(s, 1H, –CH=N–), 10.19 (s,1H, NH, D_2O exchangeable), 12.49 (s, 1H, Ar-OH, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 115.41, 115.51, 117.67, 118.51, 119.58, 123.14, 123.21, 133.43, 134.72, 138.98,138.99, 157.54, 161.68, 163.29; ESI-MS: *m/z*, 394 $[M+ H]^+$. Anal. Calcd for $C_{14}H_9Br_2N_3O$: C, 42.74; H, 2.29; N, 10.68. Found: C, 42.77; H, 2.36; N, 10.66.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)imino)methyl)-4-bromo-6-methoxyphenol, 2g: Brown solid. Yield 72%. m.p. 173-75°C. IR (KBr): 3436 (OH), 3328 (NH), 1660 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 7.13-7.88 (m, 6H, Ar-H), 8.97(s, 1H, –CH=N–), 10.19 (s,1H, NH, D_2O exchangeable), 12.45 (s, 1H, Ar-OH, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 52.34, 115.43, 115.53, 117.69, 118.53, 119.61, 123.16, 123.24, 133.45, 134.75, 138.98, 138.99, 157.56, 161.70, 165.25; ESI-MS: *m/z*, 346 $[M+ H]^+$. Anal. Calcd for $C_{15}H_{12}BrN_3O_2$: C, 52.17; H, 3.47; N, 12.17. Found: C, 52.20; H, 3.49; N, 12.15.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)imino)methyl)-5-methylphenol, 2h: Pale yellow solid. Yield 80%. m.p. 144-46°C. IR (KBr): 3402 (OH), 3322 (NH), 1648 cm^{-1} (C=N); ^{1}H NMR(300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 6.92-7.12 (m, 7H, Ar-H), 8.88 (s, 1H, –CH=N–), 10.11 (s,1H, NH, D_2O exchangeable), 12.42 (s, 1H, Ar-OH, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.26, 115.30, 115.47, 117.54, 118.47, 119.52, 123.05, 123.14, 133.38, 134.68, 138.95, 138.99, 157.41, 161.65, 164.24; ESI-MS: *m/z* 252 $[M+ H]^+$. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.71; H, 5.17; N, 16.73. Found: C, 71.73; H, 5.20; N, 16.70.

General procedure for the synthesis of 2-(((1*H*-benzo[*d*]imidazol-2-yl)amino)methyl) phenols, 3a-h

Schiff's base **2** (0.01m mol) was taken in methanol (10 mL), cooled to 10°C in an ice-bath. To this sodium borohydride (0.2 mmol) was added portion wise with stirring. After complete addition of sodium borohydride, reaction mixture was brought to room temperature and stirred for another 2-3 h. Reaction progress was monitored by TLC (50% ethyl acetate in n-hexane). Reaction mixture was concentrated under reduced pressure and the residue was washed with cold water, filtered, and washed with cold methanol, and dried under vacuum. The product was recrystallized from methanol.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)amino)methyl)-phenol, 3a: Pale yellow solid. Yield 90%. m.p. 146-48°C. IR (KBr): 3380 (NH), 3392 (NH), 3260 cm^{-1} (OH); ^1H NMR (300 MHz, $CDCl_3$): δ 4.20 (s, 2H, N-CH_2), 6.34 (s, 1H, NH, D_2O exchangeable), 6.52-7.00 (m, 8H, Ar-H), 9.50 (s, 1H, Ar-OH, D_2O exchangeable), 10.10 (s, 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 42.03, 113.34, 113.39, 116.33, 120.47, 123.92, 123.98, 127.81, 128.01, 128.99, 138.93, 138.98, 156.30, 160.56; ESI-MS: *m/z* 240 $[M+ H]^+$. Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.29; H, 5.43; N, 17.57; Found: C, 70.30; H, 5.47; N, 17.59%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)amino)methyl)-6-methoxyphenol, 3b: Pale yellow solid. Yield 92%. m,p, 153-55°C. IR (KBr): 3378 (NH), 3395 (NH), 3258 cm^{-1} (OH); ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 4.21 (s, 2H, N-CH_2), 6.37 (s, 1H, NH, D_2O exchangeable), 6.57-7.08 (m, 7H, Ar-H), 9.48 (s, 1H, Ar-OH, D_2O exchangeable), 10.09 (s, 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 42.05, 52.35, 113.36, 113.35, 116.36, 120.49, 123.96, 124.01, 127.83, 128.04, 128.99, 138.90, 138.97, 156.34, 161.39; ESI-MS: *m/z* 270 $[M+ H]^+$. Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.91; H, 5.57; N, 15.61. Found: C, 66.93; H, 5.60; N, 15.62%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)amino)methyl)-6-chlorophenol, 3c: Pale yellow solid. Yield 84%. m.p. 158-60°C. IR (KBr): 3383 (NH), 3396 (NH), 3264 cm^{-1} (OH); ^1H NMR (300 MHz, $CDCl_3$): δ 4.22 (s, 2H, N-CH_2), 6.35 (s, 1H, NH, D_2O exchangeable), 6.56-7.10 (m, 7H, Ar-H), 9.55 (s, 1H, Ar-OH, D_2O exchangeable), 10.14 (s, 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR(75MHz, $CDCl_3$): δ 42.06, 113.36, 113.41, 116.36, 120.49, 123.94, 124.01, 127.83, 128.04, 128.99, 138.95, 138.99, 156.33, 163.58; ESI-MS: *m/z*, 274 $[M+ H]^+$. Anal. Calcd for $C_{14}H_{12}ClN_3O$: C, 61.53; H, 4.39; N, 15.38. Found: C, 61.50; H, 4.40; N, 15.37%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)amino)methyl)-4,6-dichlorophenol, 3d: Pale yellow solid. Yield 82%. m.p. 165-67°C. IR(KBr): 3388 (NH), 3399 (NH), 3269 cm^{-1} (OH); ^1H NMR (300 MHz, $CDCl_3$): δ 4.25 (s, 2H, N-CH_2), 6.38 (s, 1H, NH, D_2O exchangeable), 6.59-7.17 (m, 6H, Ar-H), 9.59 (s, 1H, Ar-OH, D_2O exchangeable), 10.17 (s, 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 42.08, 113.32, 113.45, 116.32, 120.51, 123.97, 124.09, 127.88, 128.09, 129.01, 138.98, 138.99, 156.37, 166.23; ESI-MS: *m/z*, 308 $[M+ H]^+$. Anal. Calcd for $C_{14}H_{11}Cl_2N_3O$: C, 54.72; H, 3.58; N, 13.68. Found: C, 54.70; H, 3.60; N, 13.66%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)amino)methyl)-6-bromophenol, 3e: Brown solid. Yield 75%. m.p. 169-71°C. IR (KBr): 3390 (NH), 3397 (NH), 3271 cm^{-1} (OH); ^1H NMR (300 MHz, $CDCl_3$): δ 4.27 (s, 2H, N-CH_2), 6.41 (s, 1H, NH, D_2O exchangeable), 6.59-7.19 (m, 7H, Ar-H), 9.61 (s, 1H, Ar-OH, D_2O exchangeable), 10.18 (s, 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 42.10, 113.30, 113.48, 116.36, 120.54, 123.94, 124.11, 127.90, 128.12, 129.05, 138.98, 138.99, 156.39, 163.22; ESI-MS: *m/z*, 318 $[M+ H]^+$. Anal. Calcd for $C_{14}H_{12}BrN_3O$: C, 52.99; H, 3.78; N, 13.24. Found: C, 52.96; H, 3.81; N, 13.21%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)amino)methyl)-4,6-dibromophenol, 3f: Brown solid. Yield 74%. m.p. 177-78°C. IR (KBr): 3394 (NH), 3400 (NH), 3274 cm^{-1} (OH); ^1H NMR (300 MHz, $CDCl_3$): δ 4.28 (s, 2H, N-CH_2), 6.43 (s, 1H, NH, D_2O exchangeable), 6.59-7.23 (m, 6H, Ar-H), 9.64 (s, 1H, Ar-OH, D_2O exchangeable), 10.20 (s, 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 42.11, 113.32, 113.50, 116.39, 120.57, 123.98, 124.16, 127.94, 128.16, 129.09, 138.99, 139.02, 156.43, 160.25; ESI-MS: *m/z*, 396 $[M+ H]^+$. Anal. Calcd for $C_{14}H_{11}Br_2N_3O$: C, 42.53; H, 2.78; N, 10.63. Found: C, 42.50; H, 2.76; N, 10.60%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)amino)methyl)-4-bromo-6-methoxyphenol, 3g: Brown solid. Yield 77%. m.p. 183-85°C. IR (KBr): 3392 (NH), 3395 (NH), 3270 cm^{-1} (OH); ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H,

OCH_3), 4.28 (s, 2H, N-CH_2), 6.40 (s, 1H, NH, D_2O exchangeable), 6.59-7.25 (m, 6H, Ar-H), 9.64 (s, 1H, Ar-OH, D_2O exchangeable), 10.19 (s, 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 42.10, 52.35, 113.30, 113.48, 116.41, 120.59, 123.99, 124.19, 127.97, 128.90, 128.99, 138.99, 139.03, 156.46, 161.71; ESI-MS, *m/z*: 348 [M+ H]$^+$. Anal. Calcd for $C_{15}H_{14}BrN_3O_2$: C, 51.87; H, 4.03; N, 12.10. Found: C, 51.85; H, 4.06; N, 12.09%.

2-(((1*H*-Benzo[*d*]imidazol-2-yl)amino)methyl)-5-methylphenol, 3h: Pale yellow solid. Yield 90%. m.p. 149-51°C. IR (KBr): 3383 (NH), 3394 (NH), 3262 cm^{-1} (OH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 4.18 (s, 2H, N-CH_2), 6.32 (s, 1H, NH, D_2O exchangeable), 6.52-7.05 (m, 7H, Ar-H), 9.55 (s, 1H, Ar-OH, D_2O exchangeable), 10.12 (s, 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.43, 42.05, 113.37, 113.42, 116.36, 120.49, 123.94, 123.98, 127.85, 128.04, 128.99, 138.97, 138.98, 156.34, 166.32; ESI-MS: *m/z*, 254 [M+ H]$^+$. Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.14; H, 5.92; N, 16.60. Found: C, 71.10; H, 5.95; N, 16.65%..

General procedure for the synthesis of 4-(1*H*-benzo[*d*]imidazol-2-yl)-4,5-dihydrobenzo[*f*][1,4] oxazepin-3(2*H*)-ones, 4a-h

Compound **3** (0.1 m mol) was dissolved in dichloromethane (10 mL), cooled to 10°C in an ice-bath. To this chloroacetyl chloride (0.1m mol) followed by triethylamine (0.2 m mol) were added drop wise with stirring. After the complete addition, the reaction continued at 40°C for 6-8 h with stirring. Reaction progress was monitored by TLC (20% ethyl acetate in n-hexane). After completion of the reaction, as indicated by TLC reaction mixture was concentrated under reduced pressure and the residue was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, followed by brine solution, and dried over Na_2SO_4 and concentrated. The product was recrystallized from methanol**.**

4-(1*H*-Benzo[*d*]imidazol-2-yl)-4,5-dihydrobenzo-[*f*][1,4]oxazepin-3(2*H*)-one, 4a: Pale yellow solid. Yield 79%. m.p. 188-200°C. IR (KBr): 3394 (NH), 1697 cm^{-1} (NCO); ^{1}H NMR(300 MHz, $CDCl_3$): δ 4.90 (s, 2H, N-CH_2), 5.30 (s, 2H, O-CH_2), 6.80-7.18 (m, 8H, Ar-H) 10.10 (s. 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 47.88, 71.82, 114.17, 115.34, 115.47, 120.90, 123.03, 123.21, 127.88, 128.07,128.95, 138.91, 138.98, 148.45, 156.63, 171.08; ESI-MS: *m/z*, 280 [M+ H]$^+$. Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.65; N, 15.05. Found: C, 68.83; H, 4.68; N, 15.03%.

4-(1*H*-Benzo[*d*]imidazol-2-yl)-9-methoxy-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one, 4b: Pale yellow solid. Yield 82%. m.p. 195-97°C. IR(KBr): 3390 (NH), 1694 cm^{-1} (NCO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s,3H, OCH_3), 4.88 (s, 2H, N-CH_2), 5.28 (s, 2H, O-CH_2), 6.80-7.21 (m, 7H, Ar-H), 10.08 (s. 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NM (75MHz, $CDCl_3$): δ 47.83, 52.45, 71.80, 114.19, 115.37, 115.49, 120.92, 123.06, 123.25, 127.90, 128.09, 128.91, 138.95, 138.99, 148.48, 156.68, 175.05; ESI-MS: *m/z*, 310 [M+ H]$^+$. Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.85; N, 13.59. Found: C, 66.03; H, 4.88; N, 13.56%.

4-(1*H*-Benzo[*d*]imidazol-2-yl)-9-chloro-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one, 4c: Pale yellow solid. Yield 79%. m.p. 200-202°C. IR (KBr): 3397 (NH), 1699 cm^{-1} (NCO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.94 (s, 2H, N-CH_2), 5.35 (s, 2H, O-CH_2), 6.84-7.19 (m, 7H, Ar-H) 10.12 (s. 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 47.90, 71.88, 114.19, 115.36, 115.49, 120.93, 123.07, 123.23, 127.91, 128.11,128.98, 138.95, 138.98, 148.47, 156.68, 174.11; ESI-MS: *m/z*, 314[M+ H]$^+$. Anal. Calcd for $C_{16}H_{12}N_3ClO_2$: C, 61.34; H, 3.83; N, 13.41. Found: C, 61.30; H, 3.85; N, 13.39%.

4-(1*H*-Benzo[*d*]imidazol-2-yl)-7,9-dichloro-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one, 4d: Pale yellow solid. Yield 78%. m.p. 206-208°C. IR (KBr): 3399 (NH), 1670 cm^{-1} (NCO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.70 (s, 2H, N-CH_2), 5.28 (s, 2H, O-CH_2), 6.80-7.37 (m, 6H, Ar-H), 10.10(s. 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 47.91, 71.90, 114.21, 115.38, 115.51, 120.95, 123.09, 123.25, 127.93, 128.15, 128.98, 138.98, 138.98, 148.44, 156.63, 176.15; ESI-MS: *m/z*, 348 [M+ H]$^+$. Anal. Calcd for $C_{16}H_{11}Cl_2N_3O_2$: C, 55.33; H, 3.17; N, 12.10. Found: C, 55.36; H, 3.14; N, 12.09%.

4-(1*H*-Benzo[*d*]imidazol-2-yl)-9-bromo-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one, 4e: Brown solid. Yield 75%. m.p. 210-12°C. IR (KBr): 3400 (NH), 1672 cm^{-1} (NCO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (s, 2H, N-CH_2), 5.29 (s, 2H, O-CH_2), 6.80-7.39 (m, 7H, Ar-H), 10.11 (s. 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR

(75MHz, $CDCl_3$): δ 47.93, 71.92, 114.23, 115.39, 115.53, 120.97, 123.11, 123.27, 127.95, 128.18, 128.98, 138.99, 139.00, 148.45, 156.66, 178.17; ESI-MS: *m/z* 358 $[M+H]^+$. Anal. Calcd for $C_{16}H_{12}BrN_3O_2$: C, 53.78; H, 3.36; N, 11.76. Found: C, 53.75; H, 3.34; N, 11.74%.

4-(1*H*-Benzo[*d*]imidazol-2-yl)-7,9-dibromo-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one, 4f: Brown solid. Yield 74%. m.p. 214-16°C. IR (KBr): 3402 (NH), 1672 cm^{-1} (NCO); ^1H NMR (300 MHz, $CDCl_3$): δ 4.72 (s, 2H, N-CH_2), 5.30 (s, 2H, O-CH_2), 6.80-7.39 (m, 6H, Ar-H), 10.12 (s. 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 47.94, 71.95, 114.25, 115.43, 115.57, 120.99, 123.11, 123.27, 127.99, 128.16, 128.98, 138.99, 139.02, 148.47, 156.68, 174.19; ESI-MS: *m/z*, 436 $[M+H]^+$. Anal. Calcd for $C_{16}H_{11}Br_2N_3O_2$: C, 44.13; H, 2.52; N, 9.65. Found: C, 44.10; H, 2.50; N, 9.63%.

4-(1*H*-Benzo[*d*]imidazol-2-yl)-7-bromo-9-methoxy-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one, 4g: Brown solid. Yield 77%. m.p. 220-22°C. IR (KBr): 3404 (NH), 1670 cm^{-1} (NCO); ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, CH_3), 4.72 (s, 2H, N-CH_2), 5.33 (s, 2H, O-CH_2), 6.88-7.41 (m, 6H, Ar-H), 10.13 (s. 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 47.96, 52.36, 71.97, 114.27, 115.46, 115.59, 121.01, 123.16, 123.24, 127.99, 128.19, 128.95, 138.99, 139.05, 148.51, 156.70, 172.20; ESI-MS: *m/z*, 388 $[M+H]^+$. Anal. Calcd for $C_{17}H_{14}BrN_3O_3$: C, 52.71; H, 3.61; N, 10.85. Found: C, 52.75; H, 3.62; N, 10.82%.

4-(1*H*-Benzo[*d*]imidazol-2-yl)-8-methyl-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one, 4h: Pale yellow solid. Yield 79%. m.p. 196-98°C. IR (KBr): 3393 (NH), 1695 cm^{-1} (NCO); ^1H NMR(300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 4.89 (s, 2H, N-CH_2), 5.31 (s, 2H, O-CH_2), 6.80-7.19 (m, 7H, Ar-H) 10.09 (s, 1H, Benzimidazole-H, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$): δ 12.35, 47.89, 71.80, 114.14, 115.33, 115.46, 120.95, 123.06, 123.24, 127.90, 128.09, 128.92, 138.96, 138.98, 148.49, 156.67, 175.10; ESI-MS: *m/z*, 294 $[M+H]^+$; Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.62; H, 5.11; N, 14.33. Found: C, 69.64; H, 5.13; N, 14.37%.

Antibacterial activity

The antibacterial activity was done by broth dilution method[19] and expressed as minimum inhibitory concentration. The readymade nutrient broth medium (Himedia, 24 g) was suspended in distilled water (100 mL) and heated to boiling until it dissolved completely. The medium and test tubes were autoclaved at pressures of 15 lb/in^2 for 20 min. A set of sterilized test tubes with nutrient broth medium was capped with cotton plugs. The test compound **4** is dissolved in suitable solvent (acetone) and concentration of 100 µg/ mL of test compound are added in the first test tube, which is serially diluted. A fixed volume of 0.5 mL overnight culture is added in all test tubes and is incubated at 37 ºC for 24 h. After 24 h, these tubes were measured for turbidity. The minimum inhibitory concentration for bacteria was determined as the lowest concentration of the compound inhibiting the visual growth of the test cultures.

Antifungal activity

The antifungal activity was done by using agar cup bioassay method[20]. The ready made potato dextrose agar (PDA) medium (Himedia, 39g) was suspended in distilled water (100 mL), and heated to boiling until it dissolved completely. The medium and petri-dishes were autoclaved at pressure of 15 lb/ inc^2 for 20 min. The medium was poured in to sterile petri-dishes under aseptic conditions in a laminar flow chamber. When the medium in the plates solidified, 0.5 mL of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving test compounds **4** in acetone and different concentrations were made. Agar inoculated cups were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. To each cup different concentrations of test solutions were added. Controls were maintained with acetone and *Fluconazole*. The treated and the controls were kept at room temperature for 72-96 h. The minimum inhibitory concentration (MIC) was recorded in µg/ml. Three to four replicates were maintained for each treatment.

Conclusion

Synthesis of a novel series of 4-(1*H*-benzo[*d*]imidazol-2-yl)-4,5-dihydro-benzo[*f*][1,4] oxazepin-3(2*H*)ones was achieved by a simple synthetic protocol. The title compounds were screened *in vitro* for their antibacterial and antifungal activities. Compounds **4b** and **4h** exhibited good antibacterial and antifungal activity, when compared to the

standard drugs, hence they can be exploited for formulation of bactericides and fungicides after detailed study.

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