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Synthesis, Characterization and Biological Activities of Some New Pyrimidines and Isoxazoles bearing Benzofuran moiety

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Abstract: 1-(5-bromo-1-bezofuran-2-yl)-3-(substituted phenyl)-prop-2-en-1one **2a-e** were prepared by the reaction of 5-bromo-2-acetylbenzofuran **1** with different aromatic aldehydes in presence of alkali. Reaction of **2a-e** with urea, thiourea and hydroxylamine hydrochloride to gave 4-(5-bromo-1-benzofuran-2-yl)-6-(substituted phenyl)-pyrimidine-2-ol **3a-e,** 4-(5-bromo-1-benzofuran-2-yl)-6-(substituted phenyl)-pyrimidine-2-thiol **4a-e** and 3-(5-bromo-1-benzofuran-2-yl)-5-(substituted phenyl)-4, 5 dihydroisoxazole **5a-e** respectively. The characterization of all synthesized compounds was done by analytical and spectral studies.

Key words: Benzofuran, Pyrimidines, Isoxazoles, analgesic, anti-inflammatory, antibacterial, antifungal activities.

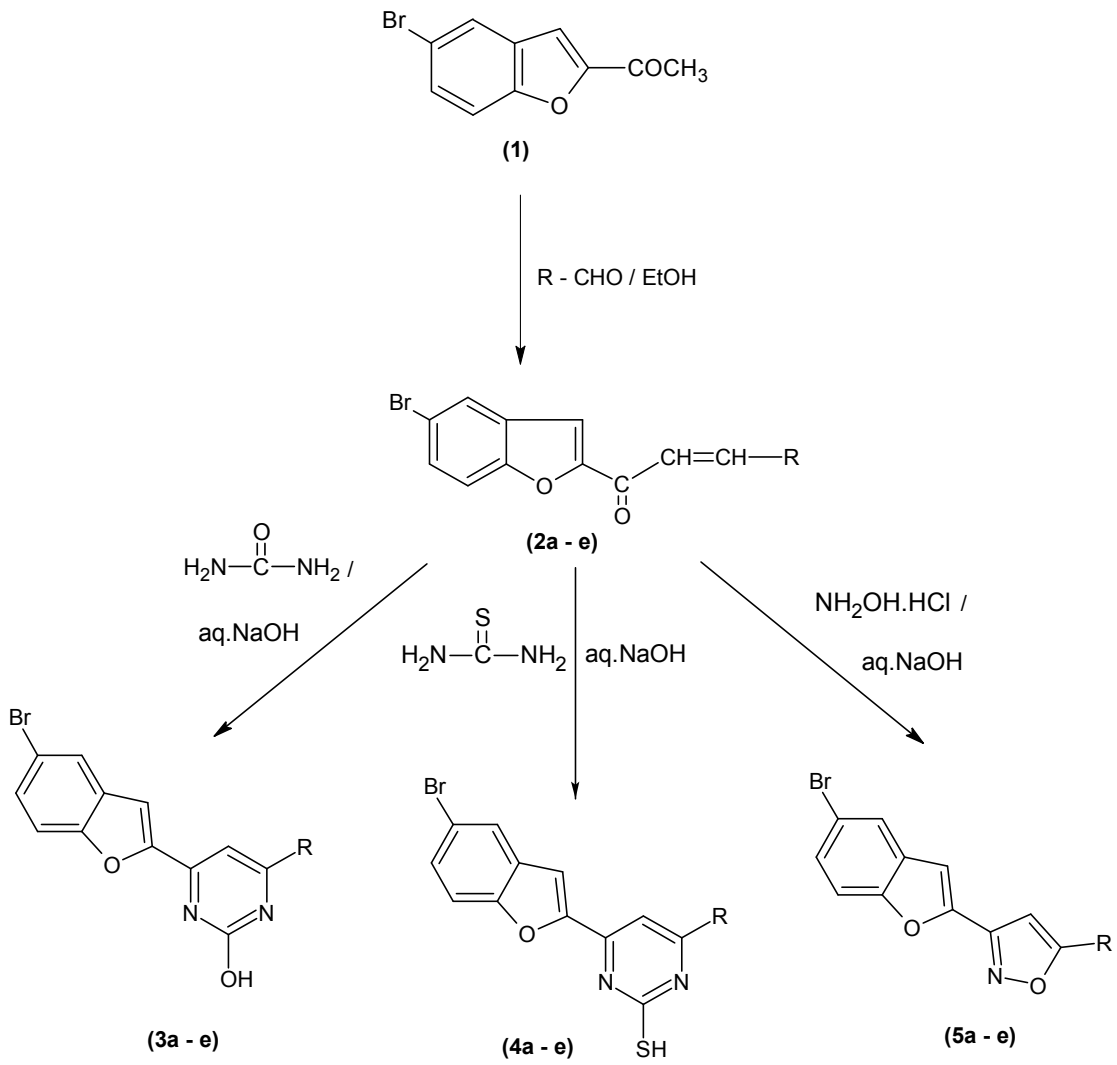
Introduction

Derivatives of Pyrimidine [1-3] and Isoxazole [4-6] have played a crucial role in the history of heterocyclic chemistry and been used extensively important pharmacophores and synthons in the field of organic chemistry. Owing to their versatile chemotherapeutic importance, a significant amount of research effort has been focused on these nuclei. Many classes of chemotherapeutic agents containing pyrimidine nucleus are in clinical use such as antibacterial agents (sulfadiazines, sulfamerazine and sulpfamethazine), anticancer (5-flurouracil and ftorafur), antiviral agents (iodoxuridine, trifluridine and zidovudine), antifungal (flucytosine) and antimalarial agents (pyrimethamine). Nitrogen containing hetrocycles such as pyrimidine and isoxazole is a promising structural moiety for drug designing. Pyrimidine based heterocycles are potential bioactive molecules and exhibit antimicrobial[7], anti-inflammatory[8], antioxidant[9], anticancer[10] antitubercular[11], antihypertensive[12], anticonvulsant[13] and also act as enzyme inhibitors. Inspired from these facts, we have attempted to synthesis some benzofuranpyrimidine and benzofuranisoxazole derivatives and evaluated for their analgesic, anti-inflammatory, antibacterial and antifungal activities.

Experimental

The melting point of all synthesized compounds were determined by open capillary tubes and are uncorrected, they are expressed in degree Celsius. Purity of all the compounds was checked by TLC using suitable solvent system. The IR spectra in KBr, (cm^{-1}) was taken on FTIR-8400S (SHIMADZU) spectrometer at the Dept. of Bulk Drugs, Karnataka College of pharmacy, Bidar. The ^{1}HNMR spectra were recorded on Mercury plus (Varian 400 MHz) Aurigene Discovery Technologies Ltd, Hyderabad; Chemical shifts are expressed in δ ppm, by using TMS as internal standard. Mass spectra were recorded by using ILS-CHU-C41-MC-IV Hyderabad. 5-bromo-2-acetylbenaofuran **1** was prepared according to reported method [14].

Scheme-1



Where	R
a	C_6H_5
b	$C_6H_4OH(p)$
c	$C_6H_4Cl(p)$
d	$C_6H_4OCH_3(p)$
e	$C_6H_4N(CH_3)_2$

Synthesis of 1-(5-bromo-1-benzofuran-2-yl)-3-(substituted phenyl)-prop-2-en-1-one (2a-e)

To a mixture of 5-bromo-2-acetyl benzofuran 2 (0.01 mol) and aromatic various substituted aldehydes (0.01 mol) in ethanol (50 mL) cooled at 5-10 ^{0}C was added aqueous sodium hydroxide (70 %, 5mL) drop wise with constant stirring. The reaction mixture was further stirred for 2h and left over night. The reaction mixture was neutralized with concentrated hydrochloric acid, and then the solid separated was collected and crystallized from suitable solvent. The purity of the compound was established by TLC using a mixture of hexane and ethyl acetate as a mobile phase.

Compound 2b: IR (KBr): 3747(OH), 1662(C=O), 1442 (C=C), 805 (C- Br). ^{1}HNMR: (δppm) 6.5 – 6.9 (d, 1H, CH=CH), (s, 1H, CO-CH), 7.0 – 8.0 (m, 8H, ArH), 9.8 (s, 1H, OH). Mass spectrum (m/z) molecular ion peak at 343 and its isotopic peak at 345.

Compound 2d: IR (KBr): 1666 (C=O), 1458 (C=C), 804 (C-Br). ^{1}HNMR (δppm), 3.7 (s, 3H, OCH_3), 6.5 – 6.8 (d, 1H, CH=CH), 7.0 – 8.0 (m, 8H, ArH). Mass spectrum (m/z) molecular ion peak at 357 and isotopic peak at 359.

Synthesis of 4-(5-bromo-1-benzofuran-2-yl)-6-(substituted phenyl)-pyrimidine-2-ol (3a-e)

To a solution of 1-(5-bromo-1-benzofuran-2-yl)-3-(substituted phenyl)-prop-2-en-1-one 8a-e (0.01 mole) in anhydrous ethanol (50 mL), urea (0.01 mole) and aqueous sodium hydroxide (0.01 mole). The reaction mixture was refluxed for 5hrs and poured into ice cold water the product obtained was filtered, washed with water and crystallized from suitable solvent. The purity of the compound was established by TLC using a mixture of hexane and ethyl acetate as a mobile phase.

Compound 3b: IR (KBr): 3747 (OH), 1542 (C = N), 1444 (C=C), 804 (C-Br). ^{1}HMNR: (δppm), 7.0 – 8.0 (m, 9H, ArH), 9.7 (s, 2H, 2 OH). Mass spectrum (m/z) molecular ion peak at 383 and isotopic peak at 385.

Compound 3d: IR (KBr): 3760 (OH), 1552 (C=N), 1442 (C=C), 806 (C-Br). ^{1}HNMR: (δppm), 3.9 (s, 3H, OCH_3), 7.0 – 8.0 (m, 9H, ArH), 9.6 (1H, OH). Mass spectrum (m/z) molecular ion peak at 397 and isotopic peak at 399.

Synthesis of 4-(5-bromo-1-benzofuran-2-yl)-6-(substituted phenyl)-pyrimidine-2-thiol (4a-e)

To a solution of 1-(5-bromo-1-benzofuran-2-yl)-3-(substituted phenyl)-prop-2-en-1-one 8a-e (0.01 mole) in anhydrous ethanol (50 mL), thiourea (0.01 mole) and aqueous sodium hydroxide (0.01 mole). The reaction mixture was refluxed for 5hrs and poured into ice cold water the product obtained was filtered, washed with water and crystallized from suitable solvent. The purity of the compound was established by TLC using a mixture of hexane and ethyl acetate as a mobile phase.

Compound 4b: IR (KBr): 3741 (OH), 1568 (C=N), 1433 (C=C), 806 (C-Br). ^{1}HNMR: (δppm), 7.0 – 8.0 (m, 9H, ArH), 9.6 (s, 1H, OH), 13.6 (s, 1H, SH). Mass spectrum (m/z) molecular ion peak at 399 and isotopic peak at 401.

Compound 4d: IR (KBr): 1548 (C=N), 1444 (C=C), 804 (C-Br). ^{1}HNMR: (δppm), 3.9 (s, 3H, OCH_3), 7.0 – 8.0 (m, 9H, ArH), 13.7 (s,1H, SH). Mass spectrum (m/z) molecular ion peak at 413 and isotopic peak at 415.

Synthesis of 3-(5-bromo-1-benzofuran-2-yl)-5-(substituted phenyl)-4, 5-dihydro isoxazole (5a-e)

To a solution of 1-(5-bromo-1-benzofuran-2-yl)-3-(substituted phenyl)-prop-2-en-1-one 8a-e (0.01 mole) and hydroxylamine hydrochloride (0.01 mole) in anhydrous ethanol (50 mL) to this add aqueous sodium hydroxide (10%, 6 mL), the reaction mixture was refluxed for 5hrs and poured into ice cold water the product obtained was filtered, washed with water and crystallized from suitable solvent. The purity of the compound was established by TLC using a mixture of hexane and ethyl acetate as a mobile phase.

Compound 5b: IR (KBr): 3747 (OH), 1561 (C=N), 1442 (C=C), 804 (C-Br). ^{1}HNMR: (δppm), 3.9 - 4.2 (d, 2H, CH_2), 6.5 (s 1H, CH), 7.0 – 8.0 (m, 8H, ArH), 9.8 (s, 1H, OH). Mass spectrum (m/z) molecular ion peak at 358 and isotopic peak at 360.

Compound 5d: IR (KBr): 1548 (C=N), 1446 (C=C), 804 (C-Br). ^{1}HNMR: (δppm), 3.4 (s, 3H, OCH_3), 3.9 - 4.2 (d, 2H, CH_2), 6.5 (s 1H, CH), 7.0 – 8.0 (m, 8H, ArH). Mass spectrum (m/z) molecular ion peak at 372 and isotopic peak at 375.

Result and Discussion

1. Analgesic activity

All the synthesized benzofuranpyrimidine and isoxazole derivatives (**3a-e, 4a-e** and **5a-e**) were evaluated for their analgesic activity employed by Eddy's hot plate method. Ibuprofen was used as a reference standard for comparison. Compound **3c, 3d, 4c, 4d, 5c** and **5d** possessed maximum activity and this may be due to the presence of 4-chlorophenyl and 4-methoxyphenyl pharmacophore at C-6 position of pyrimidine and C-5 position of isoxazole nucleus respectively. Remaining compounds showed remarkable activity. The analgesic activity results were presented in **Table-2**.

2. Anti-inflammatory activity

All the synthesized benzofuranpyrimidine and benzofuranisoxazole derivatives **(3a-e, 4a-e and 5a-e)** were evaluated for their anti-inflammatory activity by carrageenan induced rat paw oedema method. Aceclofenac was used as reference standard for comparison. In addition, it was found that compound **3c, 3d, 4c, 4d, 5c** and **5d** possessed maximum activity and this may be due to the presence of 4-chlorophenyl and 4-methoxyphenyl pharmacophore at C-6 position of pyrimidine and C-5 position of isoxazole nucleus respectively. Moreover, it was also observed that the compounds **3b, 3e, 4b, 4e, 5b** and **5e** carrying 4-hydroxyphenyl and 4-dimethylphenyl at C-6 position of pyrimidine and C-5 position of isoxazole nucleus showed remarkable activity. The analgesic activity results were presented in **Table-3**.

3. Antimicrobial activity

The newly synthesized compounds were subjected to *invitro* antibacterial activity against by Cup-Plate diffusion method using organisms *E.coli, B.subtilis* for antibacterial activity where as *A. Niger* and *C.albican* for antifungal activity. All the test compounds were prepared at the concentration of 100µg/ml in distilled DMF. The solution of ciprofloxacin and fluconazole were prepared at the concentration of 100µg/0.1ml in DMF as standard solution for comparison of antibacterial and antifungal activities and DMF was used as control for both activity, the results were presented in **Table-4**.

The compounds **3c, 3d, 4c, 4d, 5c** and **5d** possessed significant antibacterial activity against *B.subtilis, P.aeruginosa* and the remaining compounds are exhibited moderate activity against the *B.subtilis & P.aeruginosa.* In fungicidal activity the compounds **3c, 3d, 4c, 4d, 5c** and **5d** exhibited good antifungal activity against *A.niger* and *C.albican* where as remaining compounds are exhibited moderate to weak activity against the *A.niger* and *C.albican.*

Table-1: Physical data of the synthesized compounds

Comp. No	R	M P (^{0}C)	Yield (%)	Molecular formula	Solvent for Cryst…	R_f value	Found (%) (calc)		
							C	H	N
2a	C_6H_5	161	65	$C_{17}H_{11}BrO_2$	Ethanol	0.65	62.40 (62.41)	3.36 (3.39)	--
2b	$C_6H_4(OH)(p)$	157	68	$C_{17}H_{11}BrO_3$	Ethanol	0.52	59.51 (59.50)	3.20 (3.23)	--
2c	$C_6H_4(Cl)(p)$	182	70	$C_{17}H_{10}BrClO_2$	Ethanol	0.55	56.41 (56.46)	2.77 (2.79)	--
2d	$C_6H_4(OCH_3)(p)$	176	68	$C_{18}H_{13}BrO_3$	Ethanol	0.55	60.50 (60.52)	3.67 (3.67)	--
2e	$C_6H_4N(CH_3)_2(p)$	145	58	$C_{19}H_{16}BrNO_2$	Ethanol	0.52	61.61 (61.64)	4.37 (4.36)	3.75 (3.78)
3a	C_6H_5	198	68	$C_{18}H_{11}BrN_2O_2$	Ethanol	0.55	58.86 (58.88)	3.01 (3.02)	7.61 (7.63)
3b	$C_6H_4(OH)(p)$	205	63	$C_{18}H_{11}BrN_2O_3$	Ethanol	0.63	56.40 (56.42)	2.89 (2.89)	7.31 (7.31)
3c	$C_6H_4(Cl)(p)$	235	63	$C_{18}H_{10}BrClN_2O_2$	Ethanol	0.59	53.80 (53.80)	2.50 (2.51)	6.96 (6.97)
3d	$C_6H_4(OCH_3)(p)$	210	69	$C_{19}H_{13}BrN_2O_3$	Ethanol	0.60	57.40 (57.45)	3.30 (3.30)	7.01 (7.05)
3e	$C_6H_4N(CH_3)_2(p)$	240	75	$C_{20}H_{16}BrN_3O_2$	Ethanol	0.45	58.50 (58.55)	3.90 (3.93)	10.21 (1024)
4a	C_6H_5	210	70	$C_{18}H_{11}BrN_2OS$	Ethanol	0.53	56.39 (56.41)	2.90 (2.89)	7.31 (7.31)
4b	$C_6H_4(OH)(p)$	215	75	$C_{18}H_{11}BrN_2O_2S$	Ethanol	0.45	54.13 (54.15)	2.79 (2.78)	7.01 (7.02)
4c	$C_6H_4(Cl)(p)$	230	65	$C_{18}H_{10}BrClN_2OS$	Ethanol	0.65	51.73 (51.76)	2.40 (2.41)	6.71 (6.71)

4d	$C_6H_4(OCH_3)(p)$	205	70	$C_{19}H_{13}BrN_2O_2S$	Ethanol	0.44	55.23 (55.22)	3.16 (3.17)	6.77 (6.78)
4e	$C_6H_4N(CH_3)_2(p)$	250	78	$C_{20}H_{16}BrN_3OS$	Ethanol	0.46	56.33 (56.34)	3.76 (3.78)	9.87 (9.86)
5a	C_6H_5	197	70	$C_{17}H_{12}BrNO_2$	Ethanol	0.55	59.66 (59.67)	3.52 (5.53)	4.07 (4.09)
5b	$C_6H_4(OH)(p)$	210	60	$C_{17}H_{12}BrNO_3$	Ethanol	0.61	57.01 (57.00)	3.37 (3.38)	3.91 (3.91)
5c	$C_6H_4(Cl)(p)$	242	68	$C_{17}H_{11}BrClNO_2$	Ethanol	0.59	54.20 (54.21)	2.91 (2.94)	3.71 (3.72)
5d	$C_6H_4(OCH_3)(p)$	255	72	$C_{18}H_{14}BrNO_3$	Ethanol	0.47	58.05 (58.08)	3.78 (3.79)	3.75 (3.76)
5e	$C_6H_4N(CH_3)_2(p)$	261	65	$C_{19}H_{17}BrN_2O_2$	Ethanol	0.63	59.22 (59.23)	4.44 (4.45)	7.25 (7.27)

Table -2: Analgesic activity benzofuranpyrimidine and benzofuranisoxazole derivatives (3a-e),(4a-e) and (5a-e)

Comp No	**R**	**Dose (mg/kg) Per oral**	**Average (6SE) reaction time (sec.) Time after drug treatment (min)**			
			0	**30**	**60**	**90**
Control (2%gum acacia)	--	100	3.00(±0.00)	3.00(±0.05)	3.00(±0.00)	3.00(±0.05)
Standard **Ibuprofen**	--	100	3.00(±0.25)	6.25(±0.40)	9.50(±0.25)	10.50(±0.40)
3a	C_6H_5	100	3.25(±0.25)	4.00(±0.00)	4.25(±0.40)	4.25(±0.25)
3b	$C_6H_4OH(p)$	100	3.00(±0.00)	4.00(±0.25)	5.00(±0.25)	5.75(±0.00)
3c	$C_6H_4Cl(p)$	100	3.00 ±0.42)	4.75(±0.25)	5.25(±0.40)	7.00(±0.25)
3d	$C_6H_4OCH_3(p)$	100	3.00(±0.25)	4.25(±0.00)	5.55(±0.25)	7.75(±0.25)
3e	$C_6H_4N(CH_3)_2$	100	2.75(±0.00)	3.00(±0.25)	4.50(±0.25)	5.00(±0.25)
4a	C_6H_5	100	3.25(±0.00)	3.50(±0.00)	3.50(±0.00)	3.00(±0.25)
4b	$C_6H_4OH(p)$	100	3.00(±0.25)	4.50(±0.25)	5.25(±0.40)	6.50(±0.25)
4c	$C_6H_4Cl(p)$	100	3.25(±0.42)	4.00(±0.25)	6.25(±0.25)	7.75(±0.40)
4d	$C_6H_4OCH_3(p)$	100	3.00(±0.00)	4.50(±0.25)	5.00(±0.25)	5.75(±0.25)
4e	$C_6H_4N(CH_3)_2$	100	2.75(±0.40)	3.00(±0.25)	3.25(±0.00)	5.00(±0.25)
5a	C_6H_5	100	3.00(±0.40)	3.5(±0.40)	4.75(±0.25)	5.75(±0.40)
5b	$C_6H_4OH(p)$	100	3.00(±0.25)	4.50(±0.25)	5.55(±0.40)	6.00(±0.25)
5c	$C_6H_4Cl(p)$	100	3.25(±0.00)	4.25(±0.25)	6.75(±0.25)	7.00(±0.25)
5d	$C_6H_4OCH_3(p)$	100	3.00(±0.40)	3.00(±0.25)	4.75(±0.40)	4.75(±0.00)
5e	$C_6H_4N(CH_3)_2$	100	3.00(±0.48)	4.00(±0.25)	4.75(±0.00)	6.75(±0.40)

Table -3: Anti-inflammatory activity benzofuranpyrimidine and benzofuranisoxazole derivatives (3a-e), (4a-e) and (5a-e)

Comp No	R	Dose (mg/kg body weight)	Mean value (± SE) of oedema volume at different intervals		Percentage of anti-inflammation at different intervals	
			2h	4h	2h	4h
Control (2%gum acacia)	--	100	0.254 (±0.009)	0.225 (±0.007)	--	--
Standard **Aceclofenac**	--	100	0.117 (±0.0018)	0.032 (±0.003)	54.00	86.00
3a	C_6H_5	100	0.189 (±0.002)	0.135 (±0.003)	25.59	40.00
3b	$C_6H_4OH(p)$	100	0.149 (±0.007)	0.134 (±0.006)	41.33	40.44
3c	$C_6H_4Cl(p)$	100	0.123 (±0.003)	0.112 (±0.001)	51.57	50.22
3d	$C_6H_4OCH_3(p)$	100	0.132 (±0.004)	0.115 (±0.004)	48.03	48.88
3e	$C_6H_4N(CH_3)_2$	100	0.143 (±0.005)	0.141 (±0.001)	43.7	37.33
4a	C_6H_5	100	0.188 (±0.006)	0.165 (±0.005)	25.98	26.66
4b	$C_6H_4OH(p)$	100	0.139 (±0.001)	0.114 (±0.010)	45.27	49.33
4c	$C_6H_4Cl(p)$	100	0.118 (±0.003)	0.065 (±0.005)	53.54	71.11
4d	$C_6H_4OCH_3(p)$	100	0.19 (±0.010)	0.139 (±0.003)	25.19	38.22
4e	$C_6H_4N(CH_3)_2$	100	0.155 (±0.003)	0.121 (±0.002)	38.97	46.22
5a	C_6H_5	100	0.183 (±0.011)	0.131 (±0.006)	27.95	41.77
5b	$C_6H_4OH(p)$	100	0.141 (±0.007)	0.115 (±0.002)	44.48	48.88
5c	$C_6H_4Cl(p)$	100	0.129 (±0.005)	0.109 (±0.005)	49.21	51.55
5d	$C_6H_4OCH_3(p)$	100	0.172 (±0.012)	0.135 (±0.001)	32.28	40.00
5e	$C_6H_4N(CH_3)_2$	100	0.142 (±0.009)	0.113 (±0.003)	44.09	49.77

Table – 4: Antimicrobial activity of synthesized compounds (3a-e), (4a-e) and (5a-e)

Comp No	R	Zone of inhibition (in mm)			
		Concentration of 100µg/0.1ml			
		Antibacterial		Antifungal	
		B.subtilis	***P.aeruginosa***	***A.niger***	***C.albicans***
3a	C_6H_5	14	17	16	16
3b	$C_6H_4(OH)(p)$	18	18	17	17
3c	$C_6H_4(Cl)(p)$	18	19	19	18
3d	$C_6H_4(OCH_3)(p)$	18	18	18	19
3e	$C_6H_4N(CH_3)_2(p)$	15	15	16	16
4a	C_6H_5	16	14	16	17
4b	$C_6H_4(OH)(p)$	17	18	17	18
4c	$C_6H_4(Cl)(p)$	19	19	19	18
4d	$C_6H_4(OCH_3)(p)$	19	18	18	18
4e	$C_6H_4N(CH_3)_2(p)$	16	15	16	17
5a	C_6H_5	15	14	15	16
5b	$C_6H_4(OH)(p)$	16	17	17	18
5c	$C_6H_4(Cl)(p)$	16	17	21	20
5d	$C_6H_4(OCH_3)(p)$	18	18	19	19
5e	$C_6H_4N(CH_3)_2(p)$	17	17	16	17
Ciprofloxacin (Std)		20	21	----	---
Fluconazole(Std)		----	----	22	21
Control (DMF)		6	6	6	6

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