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Synthesis and anti-microbial activity of some new 5-substituted-N^1-[(*1E*)-(substituted-2-carboxo-*1H*-quinolin-3-yl)methylene]-3-phenyl-*1H*-indole-2-carbohydrzide derivatives

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ABSTRACT

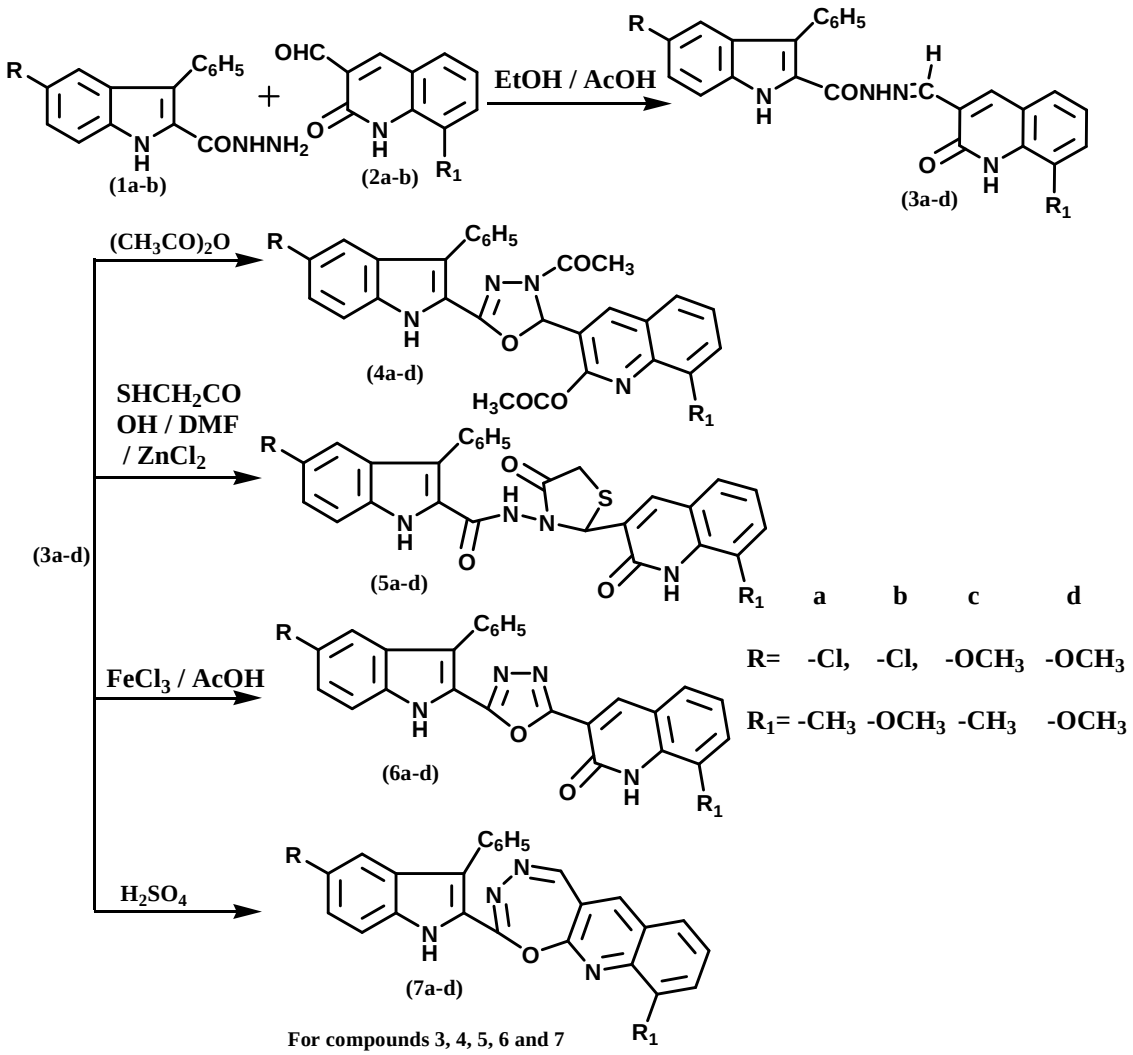
Indole and its derivatives occupied a unique place in the chemistry of nitrogen heterocyclic compounds, because of their varied biodynamic properties. New substituted indole Schiff bases 5-substituted-N^1-[(*1E*)-(substituted-2-carboxo-*1H*-quinolin-3-yl)methylene]-3-phenyl-*1H*-indole-2-carbohydrzides (3a-d) are synthesized by condensation of 5-Substituted-3-phenyl-2-carboxahydrazides (1a-b) and substituted 3-formyl-2-carboxo-*1H*-quinolines (2a-b) in presence of catalytic amount of the glacial acetic acid. These Schiff bases on further reacting with acetic anhydride/thioglycolic acid in DMF/$FeCl_3$-AcOH and con sulphuric acid gives respective pyrrazoles (4a-d)/ thioazolidines (5a-d)/ 1, 3, 4-oxadiazoles (6a-d) and oxadiazines (7a-d) indole and quinoline derivatives. All the above synthesized compounds are conformed by spectral data and elemental analysis. The newly synthesized compounds were screened for their antimicrobial activity.

KEYWORDS

Indoles;
Quinolines;
Pyrazoles;
Oxadiazoles;
Oxadiazines;
Antimicrobial activity.

INTRODUCTION

Heterocycles bearing nitrogen, sulphur and oxygen moieties constitute the core structure of a number of biologically interesting compounds. Indole nucleus is the most well known heterocyclic moiety, due to versatile biological activities. Literature survey reveals that indole and its derivatives possess wide spectrum of biological activities. In continuation of our research work on the synthesis of indole derivatives viz, antimicrobial, analgesic[1], anticatatonic[2], and anti-inflammatory[3] activities. Several indole derivatives are reported to possess antiviral[4], antihepatitis-B virus(HBV)[5] and COX-2 inhibitors[6]. Qunolines analogues have attracted great attention of medicinal and synthetic chemists because of their presence in natural products and physiological activities. There are many methods available for synthesis qunolines, the Vilsmeier approach has been recently, explored by Katritzky et. al.[7] and Srivastav et. al.[8]. In recent years, the chemistry of qunolines and their derivatives as gained increasing attention, particularly because substituted qunolines are associated with immense biological activities[8,9]. Fused indolo[2,3-c]isoquinolines possesses various biological activities such as bactericidal, fungicidal, anticancer and antihistaminic activity[10-14]. Among the wide variety of heterocycles that have been explored for developing pharmaceutically important molecules, oxadiazoles[15-18], thioazolidines[19-22] and oxadiazino[23-26] derivatives have played vital role in the medicinal chemistry. In this paper we report here the synthesis of some pyrrazole, thioazolidine, 1, 3, 4-oxadiazole and oxadiazino ring



SCHEME 1

moieties containing indole and quinoline moieties by making use of 3, 5-disubstituted indole-2-carboxyhydrazide and substituted 3-formyl-2-carboxo-*1H*-quinolines as starting materials as shown in the SCHEME 1.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on Perkin-Elmer FT-IR (spectrum 1000); ^{1}H NMR spectra on a Bruker AMX (500 MHz) spectrophotometer using DMSO or $CHCl_3$ as solvent and TMS as an internal standard (chemical shifts in δ) and mass spectra on a FAB-MS instrument. Elemental analyses were performed on an Eager 300 instrument. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapors.

Synthesis of 5-substituted-*N*^{1}-[(*1E*)-(substituted-2-carboxo-*1H*-quinolin-3-yl)methylene]-3-phenyl-*1H*-indole-2-carbohydrzides 3a-d

5-substituted-3-phenyl-2-carboxyhydrazides **(1a-b)** (0.001mol) and substituted-3-formyl-2-hydroxy-quinolines **(2a-b)** (0.001 mol) and a catalytic amount of glacial acetic acid were taken in ethanol (20 ml) and refluxed for 7-8hr on water bath. The resulting solid were filtered, washed with little alcohol dried and re-crystallized from dioxane to get 5-chloro-N^1-[(1*E*)-(substituted-2-carboxo-*1H*-quinolin-3-yl)methylene]-3-phenyl-*1H*-indole-2-carbohydrzides **(3a-d)**.

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Synthesis of 3-[(2*S*)-3-acetyl-5-(-5-susbtituted-3-phenyl-1*H*-indol-2-yl) 2, 3-dihydro-1,3,4-oxadiazol-2-yl]substituted quinolin-2-yl-acetates 4a-d

A mixture of the compounds **(3a-d)** (0.001mol) and acetic anhydride (10 ml) was refluxed for 3hr on refluxed for 3 hr on oil bath. The reaction mixture was cooled to room temperature, poured into ice-cold water and the solid separated was recrystallized from dioxane to yield 3-[(2*S*)-3-acetyl-5-(5-susbtituted-3-phenyl-*1H*-indol-2-yl) 2, 3-dihydro-1, 3, 4-oxadiazol-2-yl]substituted quinolin-2-yl acetates **(4a-d)**.

Synthesis of 5- substituted -*N*-[(2*R*)-2-(substituted-2-carboxo-*1H* quinolin-3-yl)-4-oxo-1, 3-thiazolidin-3-yl]-3-phenyl-*1H*-indole-2-carboxamides 5a-d

Compounds **(3a-d)** (0.001 mol) was refluxed in DMF (30 ml) containing a pinch of anhydrous zinc chloride and thioglycolic acid (0.001 mol) for 8hr. The reaction mixture was cooled and poured into ice cold water. The separated solid was filtered washed and recrystallized from ethanol to get 5-substituted -*N*-[(2*R*)-2-(substituted-2-carboxo-*1H*-quinolin-3-yl)-4-oxo-1, 3-thiazolidin-3-yl]-3-phenyl-*1H*-indole-2-carboxamide **(5a-d)**.

Synthesis of 2-carboxo-*1H*- 3-[5-(5-substituted-3-phenyl-*1H*-indol-2-yl)-1, 3, 4-oxadiazol-2-yl]substituted quinolines 6a-d

To a well stirred solution of compounds **(3a-d)** (0.001 mol) in acetic acid (15 ml), a solution of ferric chloride (1.5 g) in water (5 ml) was added. The mixture was stirred for 1hr and diluted with water (100) and kept at room temperature for two days. The solid separated was filtered, washed with water and recrystallized from ethanol to get compounds **(6a-d)**.

Synthesis of 2-(5-chloro-3-phenyl-*1H*-inol-2yl)[1, 3, 4]oxadiazepino[7, 6-b]substituted quinolines 7a-d

Compounds **(3a-d)** (0.001mol) were added slowly to concentrated sulphuricacid (AR grade, 0.015mol) in the cold, with stirring. The resulting mass was allowed to attain room temperature and poured into cold water. After neutralization with liquid ammonia, the product 2-(5-chloro-3-phenyl-*1H*-inol-2yl)[1, 3, 4]oxadiazepino[7, 6-b]substituted quinolines **(7a-d)** were obtained, filtered washed dried and crystallized from dioxane.

RESULTS AND DISCUSSION

Various substituted schiff's bases of indole prepared by the reaction of substituted indole-2-carboxyhydrazides **(1a-b)** with 3-formyl-1, 2-dihydroquinoline-2-ones **(2a-b)** in presence of catalytic amount of glacial AcOH under refluxed conditions gives 5-chloro-N^1-[(*1E*)-(substituted-2-hydroxyquinolin-3-yl) methylene]-3-phenyl-*1H*-indole-2-carbohydrzides **(3a-d)**. The structure of these compounds conformed by spectral data. The IR spectrum compound **(3a)** exhibited absorption peaks at 1599, 1670, 1683, 3150, 3284, and 3335 cm^{-1}, due to C=N, C=O/C=O and NH/NH/NH functions respectively. The ^{1}H NMR spectrum of **(3a)** displayed five singlets at 1.81, 6.91, 11.45, 11.67 and 12.04 due to protons of methyl group of quinoline, -CH- function, NH of indole, NH of quinoline and NH-C=O respectively. A multiplet observed in the region 7.24-8.35 is due to twelve protons of aromatic function. Mass spectral fragmentation (in m/z) of the compound **(3a)** has displayed the molecular ion peak at 454, 456 (64%, 20%). It has undergone into fragmentation to generate a fragment of peaks at 254, 256 (100%, 32%), which is the base peak of the compound. Further fragmentation is generated peaks at 219 (21%) and 190 (10%). These spectral data supports the proposed structure of compound **(3a)**. Further Cyclization of these schiff bases **(3a-d)** with acetic anhydride under refluxed conditions gave the desired 3-[(2*S*)-3-acetyl-5-(-5-chloro-3-phenyl-*1H*-indol-2-yl) 2, 3-dihydro-1, 3, 4-oxadiazol-2-yl]substituted quinolin-2-yl-acetates **(4a-d)**. The IR spectrum of substituted oxadiazole **(4a)** showed the absorption peaks at 1168, 1589, 1701, 1719 and 3348 cm^{-1}, due to cyclic C-O-C, C=N, C=O/C=O and NH functions respectively. The ^{1}H NMR spectrum showed five singlets at 1.75, 2.25, 2.29, 6.81and 11.68 due to methyl protons of quinoline moiety, two methyl protons of two ester groups, a proton of CH function and a proton of indole NH respectively. A multiplet observed in the region 7.01-7.89 is due to twelve protons of aromatic function. This further supported by the mass spectrum. Compound **(4a)** has undergone into fragmentation to

TABLE 1: Physical and spectral data of synthesized compounds

Compds	R	R^1	M.P ^{0}C (Yield%)	Spectral data* (IR (KBr)ν_{max} in cm^{-1};^{1}HNMR in δ; Mass in m/z)
3a	Cl	CH_3	275-278 (69)	1599 (C=N), 1670, 1683 (C=O/C=O), 3150, 3284, 3335 (NH/NH/NH); 1.81 (s, 3H, CH_3), 6.91 (s, 1H, 1CH), 7.24-8.35 (m, 12H, ArH), 11.45 (s, 1H, NH), 11.67 (s, 1H, NH), 12.04 (s, 1H, CONH); 454, 456(64%, 20%), 254, 256(100%, 33%), 219(21%), 191(10%).
3b	Cl	OCH_3	248-251 (69)	1599 (C=N), 1670, 1682 (C=O/C=O), 3149, 3284, 3334 (NH/NH/NH).
3c	OCH_3	CH_3	313-315 (69)	1606 (C=N), 1665, 1683 (C=O/C=O), 3150, 3287, 3313 (NH/NH/NH).
3d	OCH_3	OCH_3	343-345 (65)	1600 (C=N), 1671, 1698 (C=O/C=O), 3151, 3281, 3330 (NH/NH/NH).
4a	Cl	CH_3	187 (71)	1168 (C-O-C), 1589 (C=N), 1701, 1719 (C=O/C=O), 3348 (NH); 1.75 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 6.81(s, 1H, CH), 7.01 - 7.89 (m, 12H, ArH), 11.68(s, 1H, NH); 538, 540(35%, 10%), 495, 497(10%, 3%), 452, 454(15%,5%), 294, 296(40%, 13%), 252, 254(33%,100%).
4b	Cl	OCH_3	244(74)	1181 (C-O-C), 1610 (C=N), 1676, 1695 (C=O /C=O), 3367 (NH).
4c	OCH_3	CH_3	215(69)	1189 (C-O-C), 1605 (C=N), 1661, 1702 (C=O/C=O), 3357 (NH).
4d	OCH_3	OCH_3	195(75)	1181 (C-O-C), 1612 (C=N), 1675, 1705 (C=O/C=O), 3362 (NH).
5a	Cl	CH_3	225(75)	675 (C-S-C), 1668, 1675, 1727 (C=O /C=O/C=O),3261, 3275,3345 (NH/NH/NH); 1.74 (s, 3H, CH_3), 3.33 (s, 2H, CH_2), 6.98-8.20 (m, 13H, ArH & CH), 8.85 (s, 1H, NH), 9.15 (s, 1H, NH), 11.21 (s, 1H, CONH); 528, 530 (15%, 5%), 357, 359 (48%, 16%), 254, 256 (100%, 33%), 219 (21%), 190 (40%).
5b	Cl	OCH_3	245(64)	674 (C-S-C), 1666, 1684, 1721 (C=O /C=O/C=O), 3154, 3273, 3359 (NH/NH/NH).
5c	OCH_3	CH_3	195(76)	671 (C-S-C), 1675, 1690, 1709 (C=O /C=O/C=O), 3172, 3269, 3347 (NH/NH/NH).
5d	OCH_3	OCH_3	274(72)	677 (C-S-C), 1673, 1680, 1709 (C=O /C=O/C=O), 3164, 3229, 3340 (NH/NH/NH).
6a	Cl	CH_3	215(71)	1184 (C-O-C), 1557, 1628 (C=N/C=N), 1684 (C=O), 3248, 3322 (NH/NH); 1.75 (s, 3H, CH_3), 7.34-8.12(m, 13H, ArH), 11.47(s, 1H, NH), 12.10(s, 1H, NH); 452, 454 (34%, 12%), 424, 426 (18%,5%), 408, 410 (100%, 33%), 373 (10%).
6b	Cl	OCH_3	209(73)	1172 (C-O-C), 1543, 1608 (C=N/C=N), 1664 (C=O), 3221, 3321 (NH/NH).
6c	OCH_3	CH_3	241(76)	1176 (C-O-C), 1589, 1605 (C=N/C=N), 1674 (C=O), 3219, 3321 (NH/NH).
6d	OCH_3	OCH_3	275 (64)	1175 (C-O-C), 1578, 1612 (C=N/C=N), 1671 (C=O), 3235, 3335 (NH/NH).
7a	Cl	CH_3	240(75)	1180 (C-O-C), 1588,1604,1620 (C=N/C=N/C=N), 3309 (NH); 1.72 (s, 3H, CH_3), 6.89 (s, 1H, CH), 7.14-8.18 (m, 12H, ArH), 11.20 (s, 1H, NH); 436, 438 (48%, 16%), 266, 268(33%, 11%), 265, 267(100%, 31%), 238, 240(8%, 3%).
7b	Cl	OCH_3	197(71)	1167 (C-O-C), 1587, 1602, 1621 (C=N/C=N/C=N), 3324 (NH).
7c	OCH_3	CH_3	225(74)	1178 (C-O-C), 1596, 1605, 1624 (C=N/C=N/C=N), 3323 (NH).
7d	OCH_3	OCH_3	279(69)	1180 (C-O-C), 1582, 1605, 1618 (C=N/C=N/C=N), 3327 (NH).

***All the compounds gave satisfactory analysis for C, H and N.**

generate a fragment of molecular ion peak at m/z 538, 540 (35%, 10%), other fragmented peaks are at 495, 497(10%, 3%), 452, 454 (15%, 5%), 296, 298(40%, 13%) and 252, 254 (100%, 33%) which is the base peak of the compound. Further these schiff bases **(3a-d)** on reaction with thioglycolic acid in presence of catalytic amount of $ZnCl_2$, DMF as solvent used, furnishes the thioazolidine derivatives 5-chloro-*N*-[(2*R*)-2-(substituted-2-hydroxyquinolin-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-3-phenyll-1*H*-indole-2-carboxamides **(5a-d)**. The formation these compounds conformed by spectral data. The IR spectrum of **(5a)** shows peaks at 675,

1668, 1675, 1727, 3261, 3275 and 3345cm^{-1} due to C-S-C, C=O/C=O/C=O and NH/NHNH respectively. Its ^{1}H NMR spectrum shows the five distinct singlets at 1.74, 3.33, 8.85, 9.15 and 11.21 are due to methyl protons of quinoline moiety, methylene protons of thiazolidine moiety, indole NH, a proton of quinoline NH and amide proton respectively. A multiplet observed in the region 6.98-8.20 is due to twelve protons of aromatic function and a proton CH of thiazolidine function. Mass spectral fragmentation of the compound **(5a)** has displayed the molecular ion peak at m/z 528, 530 (15%, 5%). It has undergone into fragmentation to generate a fragment of peaks at m/z 357, 359 (48%, 16%), 254, 256 (100%, 33%), which is the base peak of the compound. Further fragmentation is generated peaks at m/z 219 (21%) and 190 (40%).

The compounds **(3a-d)** on reaction with $FeCl_3$ in presence of acetic acid under stirring at room temperature gives the substituted oxadiazole derivatives 3-[5-(5-chloro-3-phenyl-*1H*-indol-2-yl)-1, 3, 4-oxadiazol-2-yl]substituted quinolin-2-ones **(6a-d)**, these further conformed by the spectral studies. The IR spectrum of compound **(6a)** gives absorption peaks at 1184, 1557, 1628, 1684, 3248 and 3322 cm^{-1} due to the C-O-C, C=N/C=N of oxadiazole, C=O, NH/NH respectively. The ^{1}H NMR (in δ) spectrum showed three singlets at 1.75, 11.47 and 12.10 due to the protons of methyl fuction, a proton of NH of indole and NH of quinoline respectively. A multiplet due to twelve protons of aromatic function at 7.34-8.12 δ. Mass spectral fragmentation of the compound **(6a)** has displayed the molecular ion peak at m/z 452, 454 (34%, 12%). It has undergone into fragmentation to generate a fragment of peaks at m/z 424, 426 (18%, 5%), 408, 410 (100%, 32%), which is the base peak of the compound. Further fragmentation is generated peak at m/z 373 (10%). The schiff bases **(3a-d)** which on cyclization with Conc.H_2SO_4 yielded 2-(5-chloro-3-phenyl-*1H*-indol-2-yl)-1, 3, 4-oxadiazepino[7, 6-b]substituted quinolines **(7a-d)**. These oxadiazino derivatives conformed by spectral data. The IR spectrum of **(7a)** showed peaks at 1180, 1588, 1604, 1620 and 3309cm^{-1} due to C-O-C, C=N/C=N/C=N and NH of indole respectively. The ^{1}H NMR spectrum (in δ) showed three singlets at 1.72, 6.89 and 11.20 are due to the protons of methyl function, a proton of CH of oxadiazepino moiety and a proton of indole NH. A multiplet observed at 7.14-8.18δ due to twelve aromatic protons. Mass spectral fragmentation of the compound **(7a)** has displayed the molecular ion peak at m/z 436, 438 (48%, 16%). It has undergone into fragmentation to generate a fragment of peaks at m/z 265, 267 (100%, 32%), which is the base peak of the compound. These spectral data supports the proposed structure of compound **(7a)**.

Antimicrobial activity

Antimicrobial activities of synthesized compounds have been tested for their antibacterial activity against *S.aureus*, *E.coli* and *B.substilus* and antifungal activity against *A.niger* and *C.albicans* by cup-plate method[1-3]. Gentamycin and Nystatin were used as standards for antibacterial and antifungal activities respectively. The compounds were tested at the concentration of 100μg/ml in DMF for both antibacterial and antifungal activity. The zone of inhibition after 24hr of incubation at 37^{0}c, in case of antibacterial activity and 72hr in case of antifungal activity was compared with that of standards. The results are tabulated in the TABLE 2.

TABLE 2 : Anti-microbial activity of the synthesized compounds

Compds.	Concc-^{n} (μg/ml) in DMF	Zone of inhibition in mm*				
		Antibacterial activity			Antifungal activity	
		S.aureus	*E.coli*	*B.subtilus*	*A.niger*	*C.albicans*
3a	1000	15	17	16	15	17
3b	1000	18	19	18	18	20
3c	1000	11	10	10	11	13
3d	1000	12	14	12	14	15
4a	1000	17	18	19	20	19
4b	1000	15	16	13	14	15
4c	1000	15	13	14	15	13
4d	1000	12	14	15	10	10
5a	1000	16	15	17	14	15
5b	1000	17	18	15	13	15
5c	1000	15	12	13	12	14
5d	1000	12	13	09	11	14
6a	1000	18	17	19	18	19
6b	1000	15	15	14	13	14
6c	1000	14	16	14	15	13
6d	1000	11	12	14	11	13
7a	1000	16	18	19	18	18
7b	1000	15	16	17	18	17
7c	1000	11	12	15	13	11
7d	1000	10	15	12	14	16
Gentamycin	1000	22	20	21	-	-
Nystatin	1000	-	-	-	22	21
Control (DMF)		-	-	-	-	-

***Diameter of well (bore size) - 6 mm**

The results were showed that the compounds **(3b)**, **(4a)**, **(5b)** and **(6a)** showed good activity, compounds **(3a)**, **(4b)**, **(4c)**, **(5a)**, **(6c)**, **(7a)** and **(7d)** exhibited

comparable activity with Gentamycin against *S. aureus*. Compounds **(3a)**, **(3b)**, **(4a)**, **(5b)**, **(6a)** and **(7a)** showed good activity, compounds **(3d)**, **(4b)**, **(4d)**, **(5a)**, **(6b)**, **(6c)**, **(7b)** and **(7d)** exhibited comparable activity with Gentamycin against *E. coli*. Compounds **(3b)**, **(4a)**, **(5a)**, **(6a)**, **(7a)** and **(7b)** showed good activity, compounds **(3a)**, **(4c)**, **(4d)**, **(5b)**, **(6b)**, **(6c)**, **(6d)** and **(7c)** exhibited comparable activity with Gentamycin against *B. substilus*. Compounds **(3b)**, **(4a)**, **(6a)**, **(7a)** and **(7b)** showed good activity, compounds **(3a)**, **(3d)**, **(4b)**, **(4c)**, **(5a)**, **(6c)** and **(7d)** exhibited comparable activity with Nystatin against *A. niger*. Compounds **(3a)**, **(3b)**, **(4a)**, **(6a)**, **(7a)** and **(7b)** showed good activity, compounds **(3d)**, **(4b)**, **(5a)**, **(5b)**, **(5c)**, **(5d)**, **(6b)** and **(7d)** exhibited comparable activity with Nystatin against *C. albicans.*

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