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SYNTHESIS AND BIOLOGICAL EVALUATION OF N-ARYLPYRAZOLE FUSED 7-AZAINDAZOLE DERIVATIVES AS ANTIBACTERIAL AGENTS

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Abstract: A new series of N-arylpyrazolo-7-azaindole derivatives (8a-j) and their structures were synthesised and confirmed by ^{1}HNMR, ^{13}CNMR and mass spectral analysis. Further, all these newly compounds were evaluated for their antibacterial activity against both gram negative (Pseudomonas aeruginosa, Escherichia coli) and gram positive (Bacillus subtilis, Staphylococcus aureus) bacterial strains.

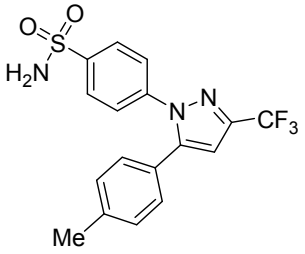
Keywords: Celecoxib, SC-558, azaindazole and antibacterial activity.

Introduction

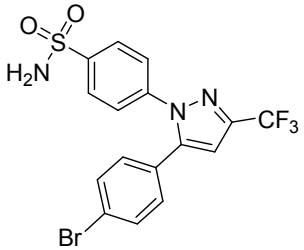
The indazole nucleus has been deemed as an important moiety found in many pharmacologically active compounds. It constitute an important class of compounds that displays an interesting biological activities such as anti-inflammatory,[I] antitumor,[II] antidepressant,[III] analgesic, antipyretic,[IV] dopamine antagonistic,[V] anti-HIV activities,[VI] antifungal[VII] and antiemetic.[VIII] Similarly, the 7-azaindazoles and their derivatives exhibit significant biological activities[IX-XII] and the use of this framework has contributed to the generation of new therapeutic agents.

Among the wide variety of nitrogen heterocyclic compounds, pyrazole derivatives are one of the most important five member heterocyclic molecules. Pyrazole derivatives occupy a distinct place in medicinal as well as combinatorial chemistry[XIII] due to their capability to exhibit an array of bioactivities such as antimicrobial,[XIV] anticancer,[XV] anti-inflammatory,[XVI] antidepressant,[XVII] anticonvulsant,[XVIII] antipyretic,[XIV] enzyme inhibitory activity[XX] antifungal[XXI] and antibacterial activities.[XXII] Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals.[XXIII] Celecoxib (**1**) and SC-558 (**2,** Figure 1) were a pyrazole nucleus containing anti-inflammatory drugs and known to inhibit COX-2 enzyme.[XXIV] Celecoxib (**1**) was also used in cancer therapy and proliferation of HCC cell lines.[XXV,XXVI]

In view of their broad biological activities of azaindazole and pyrazole to know the combined effect of both moieties it was considered worthwhile to synthesize certain new chemical entities having azaindazole and pyrazole in a single molecular framework. We report the synthesis of a series of *N*-arylpyrazole fused 7-azaindazole derivatives (**8a-j**).



Celecoxib (1)



SC-558 (2)

Material and Methods

Chemistry

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. ^{1}HNMR and ^{13}CNMR spectra were recorded Varian-NMR-Inova (500 MHz) instrument. Chemical shifts (d) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electrothermal melting point apparatus, and are uncorrected.

*5-Bromo-1H-pyrazolo[3,4-b]pyridine-3-carbaldehyde (**4**)*

In a 250 mL round bottom flask was taken compound (**3**) (10 g, 50.49 mmol), hexamethylenetetramine (HMTA) (42 g, 302.9 mmol), 40 mL acetic acid, 80 mL of H_2O, and heated to reflux for 12 hours. After the reaction solution was cooled to room temperature, a large number of solid precipitation, filtration, and the filter cake washed with water and dried to give a white solid. The crude compound obtained was recrystallized from hexane to get the pure compound **4**, 10.6 g with 90% in yield. ^{1}H NMR (DMSO-d6, 500 MHz,): δ 8.47 (d, 1H, *J* = Hz), 8.53 (d, 1H, *J* = Hz), 9.92 (s, 1H), 12.9 (s, 1H), MS (ESI): 225 [M-H].

*General procedure for synthesis of compounds (**6a,b**)*

The compound (**4**) (17.6 mmol) was dissolved in 5 mL of ethanol, followed by addition of substituted acetophenones (**5a,b**) (17.6 mmol) and two drops of piperidine. The reaction mixture was heated under reflux for 6 hours. After cooling water (20 mL) was added slowly. The crystalline precipitate was separated by filtration and purified by recrystallization from ethanol to afford pure compounds (**6a,b**).

*(E)-3-(5-Bromo-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-(pyridin-4-yl)prop-2-en-1-one **(6a)***

This compound **6a** was prepared by general method, employing **4** (4 g, 17.6 mmol), 4-acetylpyridine (**5a**) (1.9 ml, 17.6 mmol) in ethanol (20 mL) and two drops of piperidine to afford the pure compound **6a**. Yellow solid, 4.7 g with 81% in yield; Mp. 263-264 °C; ^{1}H NMR (DMSO-d6, 500 MHz,): δ 7.71 (d, 1H, *J* = 15.2 Hz), 8.01-8.07 (m, 2H), 8.41-8.45 (m, 2H), 8.90-8.98 (m, 3H), 12.60 (s, 1H); MS (ESI): 329 $[M+H]^{+}$.

*(E)-3-(5-Bromo-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-(pyridin-3-yl)prop-2-en-1-one **(6b)***

This compound **6b** was prepared by the method described for **6a**, employing **4** (4 g, 17.6 mmol), 3-acetylpyridine (**5b**) (1.9 ml, 17.6 mmol) in ethanol (20 mL) and two drops of piperidine to afford the pure compound **6b**. Yellow solid, 4.9 g with 84% in yield; Mp. 265-267 °C; ^{1}H NMR (DMSO-d6, 500 MHz,): δ 7.59-7.62 (m, 1H), 7.71 (d, 1H, *J* = 15.2 Hz), 8.01 (d, 1H, *J* = 15.8 Hz), 8.41 (d, 1H, *J* = 1.83 Hz), 8.48 (d, 1H, *J* = 7.93 Hz), 8.83-8.81 (q,

1H), 8.91 (d, 1H, *J* = 1.83 Hz), 9.37 (d, 1H, *J* = 1.22 Hz), 12.60 (s, 1H), MS (ESI): 329 $[M+H]^+$.

*General procedure for synthesis of N-arylpyrazole fused 7-azaindazole derivatives **(8a-j)***

A mixture of compounds **6a,b** (6.09 mmol) in methanol (15 mL) to added substituted phenyl hydrazine hydrogen chlorides (**7a-e**) (6.09 mmol) and 5 drops of acetic acid was refluxed for 12 hours. The completion of the reaction was monitored by TLC. The reaction mixture was allowed to cool down to room temperature and poured into ice cooled water with constant stirring. The resulting precipitate was filtered, washed with water, dried and recrystallized from methanol to afford pure compounds **8a-j**.

*5-Bromo-3-(1-phenyl-3-(pyridin-4-yl)-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine **(8a)***

This compound **8a** was prepared by general method, employing **6a** (200 mg, 6.09 mmol), phenylhydrazine hydrochloride (**7a**) (88 mg, 6.09 mmol) in methanol (10 mL) and five drops of acetic acid to afford the pure compound **8a**, 196 mg in 77% yield. ^{1}HNMR (DMSO-d6, 500 MHz): δ 6.92-6.95 (m, 1H), 7.16 (d, 1H, *J* = 8.14 Hz), 7.22-7.29 (m, 2H), 7.31-7.35 (m, 1H), 7.64 (d, 1H, *J* = 8.14 Hz), 8.03-8.10 (m, 2H), 8.21 (s, 1H), 8.29-8.33 (m, 1H), 8.75 (d, 2H, *J* = 8.24 Hz), 8.83-8.86 (m, 2H), 12.48 (s, 1H); ^{13}CNMR (DMSO-d6, 500 MHz): δ 111.1, 111.6, 111.7, 112.9, 114.0, 116.6, 119.0, 119.1, 121.2, 122.0, 123.7, 129.0, 129.8, 137.8, 139.6, 141.8, 144.3, 147.5, 148.0, 149.6, 153.5; MS (ESI): 418 $[M+H]^+$.

*5-Bromo-3-(1-(2,6-dichlorophenyl)-3-(pyridin-4-yl)-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine **(8b)*** This compound **8b** was prepared by the method described for **8a**, employing **6a** (200 mg, 6.09 mmol), 2,6-dichlorophenylhydrazine hydrochloride (**7b**) (130 mg, 6.09 mmol) in methanol (10 mL) and five drops of acetic acid to afford the pure compound **8b**, 209 mg in 71% yield. ^{1}HNMR (DMSO-d6, 500 MHz): δ 7.16-7.29 (m, 2H), 7.58 (d, 2H, *J* = 7.34 Hz), 8.01-8.05 (m, 2H), 8.38 (s, 1H), 8.72-8.77 (m, 2H), 9.77 (s, 1H), 12.45 (s, 1H); ^{13}CNMR (DMSO-d6, 500 MHz): δ 111.4, 111.9, 119.0, 123.9, 127.3, 129.2, 130.2, 137.7, 139.8, 141.8, 143.5, 147.5, 153.3; MS (ESI): 488 $[M+2]^+$.

*5-Bromo-3-(1-(3-(trifluoromethyl)phenyl)-3-(pyridin-4-yl)-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine **(8c)*** This compound **8c** was prepared by the method described for **8a**, employing **6a** (200 mg, 6.09 mmol), 3-trifluoromethylphenylhydrazine hydrochloride (**7c**) (129 mg, 6.09 mmol) in methanol (10 mL) and five drops of acetic acid to afford the pure compound **8c**, 199 mg in 67% yield. ^{1}HNMR (DMSO-d6, 500 MHz): δ 7.07-7.28 (m, 2H), 7.46-7.66 (m, 3H), 7.92-8.01 (m, 3H), 8.38 (s, 1H), 8.74-8.85 (m, 2H), 10.66 (s, 1H); ^{13}CNMR (DMSO-d6, 500 MHz): δ 109.5, 111.7, 111.9, 113.1, 116.2, 117.0, 118.9, 123.6, 130.2, 130.7, 141.5, 143.5, 145.5, 145.8, 147.6; MS (ESI): 486 $[M+H]^+$.

*5-Bromo-3-(1-(2-chlorophenyl)-3-(pyridin-4-yl)-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine **(8d)*** This compound **8d** was prepared by the method described for **8a**, employing **6a** (200 mg, 6.09 mmol), 2-chlorophenylhydrazine hydrochloride (**7d**) (109 mg, 6.09 mmol) in methanol (10 mL) and five drops of acetic acid to afford the pure compound **8d**, 220 mg in 80% yield. ^{1}HNMR (DMSO-d6, 500 MHz): δ 7.00-7.04 (m, 1H), 7.22 (s, 1H), 7.31 (s, 1H), 7.44-7.49 (m, 1H), 7.60-7.64 (m, 1H), 8.05 (s, 1H), 8.22-8.26 (m, 2H), 8.32 (s, 1H), 8.79 (s, 1H), 8.94 (s, 1H), 12.31 (s, 1H); ^{13}CNMR (DMSO-d6, 500 MHz): δ 111.2, 112.0, 115.9, 118.9, 122.4, 123.9, 128.2, 129.5, 130.4, 130.5, 131.9, 139.8, 141.2, 142.2, 143.6, 147.6, 152.5; MS (ESI): 454 $[M+2]^+$.

*5-Bromo-3-(1-(2,4-dichlorophenyl)-3-(pyridin-4-yl)-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine **(8e)*** This compound **8e** was prepared by the method described for **8a**, employing **6a** (200 mg, 6.09 mmol), 2,4-dichlorophenylhydrazine hydrochloride (**7e**) (130 mg, 6.09 mmol) in methanol (10 mL) and five drops of acetic acid to afford the pure compound **8e**, 221 mg in 75% yield. ^{1}HNMR (DMSO-d6, 500 MHz): δ 7.16 (d, 1H, *J* = 7.26 Hz), 7.35-7.42 (m, 2H), 7.57-7.62 (m, 2H), 8.02 (d, 1H, *J* = 8.23 Hz), 8.38 (d, 1H, *J* = 8.28 Hz), 8.75-8.80

(m, 2H), 9.01 (s, 1H), 9.35 (s, 1H); ^{13}CNMR (DMSO-d6, 500 MHz): δ 111.3, 112.1, 117.0, 118.9, 119.5, 121.6, 124.2, 124.7, 125.1, 127.5, 128.2, 128.8, 130.4, 130.6, 132.0, 139.3, 142.4, 142.9, 143.6, 147.6, 152.2; MS (ESI): 488 $[M+2]^+$.

5-Bromo-3-(1-phenyl-3-(pyridin-3-yl)-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine ***(8f)*** This compound **8f** was prepared by the method described for **8a**, employing **6b** (200 mg, 6.09 mmol), phenylhydrazine hydrochloride (**7a**) (88 mg, 6.09 mmol) in methanol (10 mL) and five drops of acetic acid to afford the pure compound **8f**, 201 mg in 79% yield. ^{1}HNMR (DMSO-d6, 500 MHz): δ 6.97-7.09 (m, 3H), 7.13-7.23 (m, 4H), 7.67 (s, 1H), 7.96 (s, 1H), 8.23 (s, 1H), 8.78 (d, 1H, *J* = 8.12 Hz), 9.08 (s, 1H), 11.97 (s, 1H); ^{13}CNMR (DMSO-d6, 500 MHz): δ 110.7, 113.7, 114.4, 119.5, 120.6, 121.3, 122.5, 126.4, 128.8, 129.6, 140.2, 143.5, 145.5, 148.6; MS (ESI): 418 $[M+H]^+$.

5-Bromo-3-(1-(2,6-dichlorophenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine ***(8g)*** This compound **8g** was prepared by the method described for **8a**, employing **6b** (200 mg, 6.09 mmol), 2,6-dichlorophenylhydrazine hydrochloride (**7b**) (130 mg, 6.09 mmol) in methanol (10 mL) and five drops of acetic acid to afford the pure compound **8g**, 215 mg in 73% yield. ^{1}HNMR (DMSO-d6, 500 MHz): δ 7.23 (t, 1H), 7.29 (d, 2H, *J* = 8.13 Hz), 7.33-7.37 (m, 2H), 7.68 (s, 1H), 8.19-8.25 (m, 2H), 8.60 (s, 1H), 8.97 (s, 1H), 11.94 (s, 1H); ^{13}CNMR (DMSO-d6, 500 MHz): δ 110.2, 111.2, 119.8, 124.2, 127.0, 128.9, 129.3, 134.3, 138.5, 142.6, 145.6, 147.0, 156.8; MS (ESI): 488 $[M+2]^+$.

5-Bromo-3-(1-(3-(trifluoromethyl)phenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine ***(8h)*** This compound **8h** was prepared by the method described for **8a**, employing **6b** (200 mg, 6.09 mmol), 3-trifluoromethylphenylhydrazine hydrochloride (**7c**) (129 mg, 6.09 mmol) in methanol (10 mL) and five drops of acetic acid to afford the pure compound **8h**, 191 mg in 65% yield. ^{1}HNMR (DMSO-d6, 500 MHz): δ 7.02-09 (m, 2H), 7.19-7.27 (m, 4H), 8.03 (s, 1H), 8.46 (s, 1H), 8.62 (s, 1H), 8.82 (s, 1H), 9.01 (s, 1H), 11.93 (s, 1H); ^{13}CNMR (DMSO-d6, 500 MHz): δ 109.0, 111.8, 111.9, 112.8, 113.8, 115.5, 116.7, 119.0, 125.6, 130.0, 130.3, 136.1, 141.1, 143.6, 145.8; MS (ESI): 486 $[M+H]^+$.

5-Bromo-3-(1-(2-chlorophenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine ***(8i)*** This compound **8i** was prepared by the method described for **8a**, employing **6b** (200 mg, 6.09 mmol), 2-chlorophenylhydrazine hydrochloride (**7d**) (109 mg, 6.09 mmol) in methanol (10 mL) and five drops of acetic acid to afford the pure compound **8i**, 216 mg in 79% yield. ^{1}HNMR (DMSO-d6, 500 MHz): δ 6.99-7.03 (m, 1H), 7.04 (d, 1H, *J* = 7.28 Hz), 7.21-7.29 (m, 2H), 7.34 (s, 1H), 7.61 (s, 1H), 7.84 (d, 1H, *J* = 8.13 Hz), 8.19 (d, 1H, *J* = 8.13 Hz), 8.28 (s, 1H), 8.56 (s, 1H), 9.08 (s, 1H), 11.87 (s, 1H); ^{13}CNMR (DMSO-d6, 500 MHz): δ 110.4, 112.2, 118.8, 123.1, 124.6, 124.9, 125.0, 126.8, 127.2, 129.1, 129.9, 134.8, 142.0, 142.6, 145.1, 146.8, 147.5; MS (ESI): 452 $[M+H]^+$.

5-Bromo-3-(1-(2,4-dichlorophenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine ***(8j)*** This compound **8j** was prepared by the method described for **8a**, employing **6b** (200 mg, 6.09 mmol), 2,4-dichlorophenylhydrazine hydrochloride (**7e**) (130 mg, 6.09 mmol) in methanol (10 mL) and five drops of acetic acid to afford the pure compound **8j**, 206 mg in 69% yield. ^{1}HNMR (DMSO-d6, 500 MHz): δ 7.13-7.19 (m, 1H), 7.28-36 (m, 2H), 7.58-7.67 (m, 2H), 8.05 (s, 1H), 8.31 (s, 1H), 8.66-8.75 (m, 2H), 9.06 (s, 1H), 9.29 (s, 1H), 12.28 (s, 1H); ^{13}CNMR (DMSO-d6, 500 MHz): δ 111.5, 112.0, 113.1, 116.6, 118.9, 124.0, 126.1, 128.1, 128.6, 130.8, 131.7, 136.1, 140.1, 143.3, 143.5, 147.6; MS (ESI): 488 $[M+2]^+$.

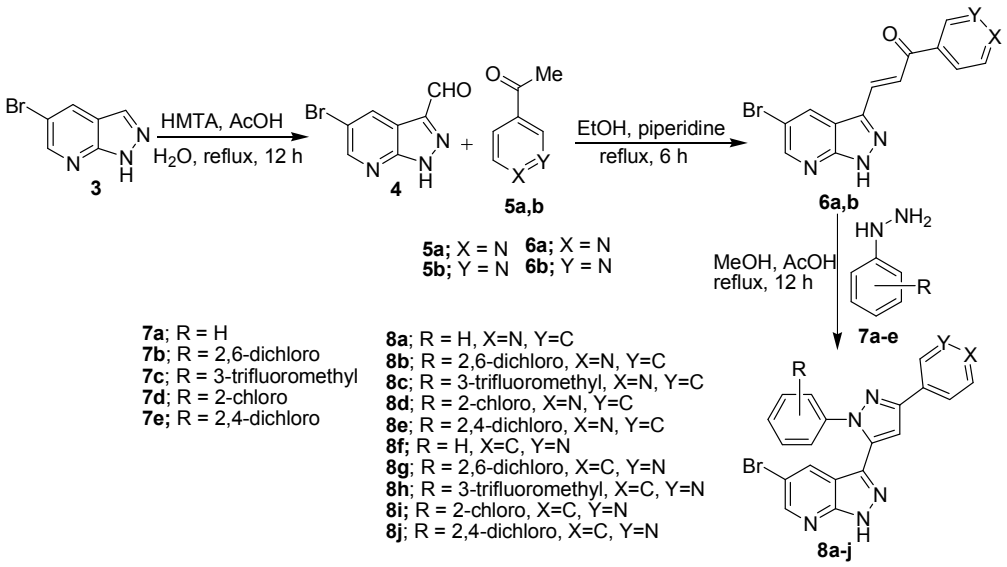
Result and Discussion

Chemistry

The newly target compounds (**8a-j**) were synthesized by multistep as shown in Scheme 1. Compound 5-bromo-1H-pyrazolo[3,4-b]pyridine (**3**) was reacted with

hexamethylenetetramine (HMTA) in acetic acid and H_2O at reflux for 12 hours to afford pure aldehyde compound **4**, then it was subjected to aldol condensation with different substituted acetophenones (**5a,b**) in ethanol and catalytic amount of piperidine at reflux for 6 hours to gave pure chalcone derivatives (**6a,b**) in good yield. Finally these chalcone (**6a,b)** intermediates was reacted with different substituted phenylhydrazine hydrochlorides (**7a-e**) in methanol and acetic acid at reflux for 12 hours to afford pure N-aryl pyrazole derivatives (**8a-j).**

Scheme 1.



Biological Evaluation

Antibacterial Activity

These novel target compounds (**8a-j**) were evaluated for their antibacterial activity against both gram negative (*Pseudomonas aeruginosa*, *Escherichia coli*) and gram positive (*Bacillus subtilis*, *Staphylococcus aureus)* bacterial strains. These results are summarized in Table 1 and Zentamycine was used as positive control. Most of the synthesized compounds exhibited satisfactory zone of inhibitory activity comparing with reference drug.

Table 1. Zone of inhibition of target compounds (**8a-j)** in mm.

Compd	Gram Nagative (-Ve)				Gram Positive (+Ve)			
	Control	***Pseudomonas aeruginosa***	**Control**	***Escherichia coli***	**Control**	***Bacillus subtilis***	**Control**	***Staphylococcus aureus***
8a	12	3	10	2.5	15	2.5	10	2.5
8b	12	3	10	3	15	2.5	10	3
8c	12	6	10	4	15	5	10	7
8d	12	7	10	4	15	8	10	7
8e	12	5	10	2.5	15	3	10	6
8f	12	5	6	2.5	10	5	12	5
8g	12	4	6	2.5	10	2.5	12	2.5
8h	12	4	6	2.5	10	5	12	4
8i	12	8	6	2.5	10	9	12	7
8j	12	5	6	2.5	10	2.5	12	4

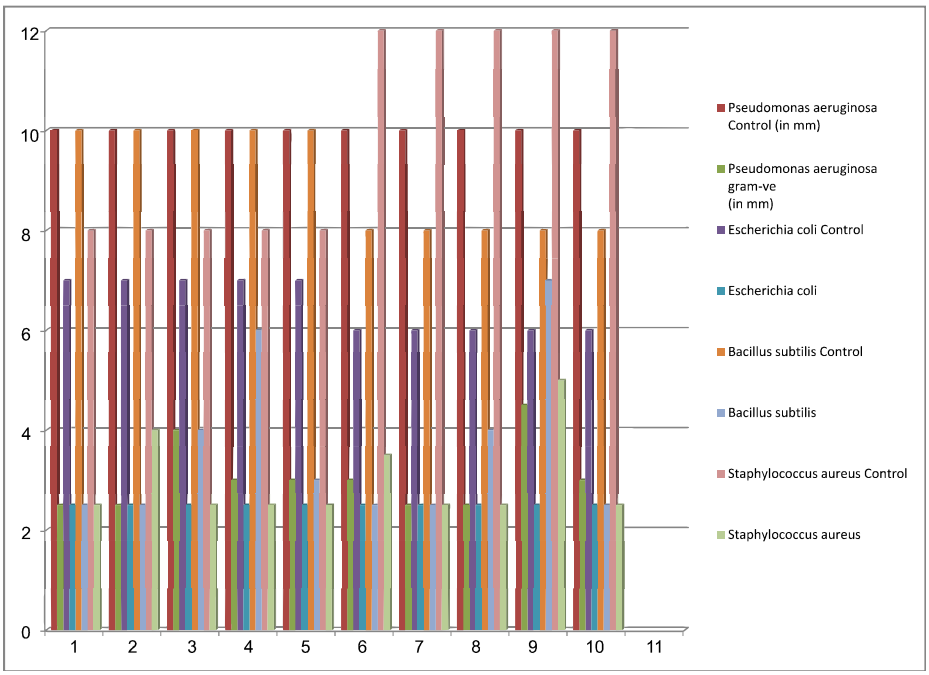


Figure 2.

Conclusion

In summary, we have synthesized a new series of *N*-arylpyazolo-7-azaindole derivatives (**8a-j**). All these derivatives were evaluated for their antibacterial activity against both two gram negative (*Pseudomonas aeruginosa*, *Escherichia coli*) and gram positive (*Bacillus subtilis*, *Staphylococcus aureus)* bacterial strains. Here Gentamycin was used as positive control. Most of the compounds were exhibited potent antibacterial activity. The compounds 8c, 8d and 8i are most potent among other derivatives.

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