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Eco-Friendly, Green Approach for Synthesis of Bio-Active Novel 3-Aminoindazole Derivatives

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Abstract

In present chapter we have reported green and highly efficient method for synthesize novel series of substituted -1H-indazol-3-amine derivative (**3a-h**) by cyclocondensation reaction of substituted benzonitrile (**1a-h**) and substituted Hydrazine (**2a-h**) using ceric (IV) ammonium nitrate (CAN) as a catalyst, EtOH-H₂O as a ecofriendly media and reaction was carried out under ultrasound irradiation green method. The structures of newly synthesized indazole derivative (**3a-h**) were corroborated through spectral investigation such as elemental analysis and spectral studies like IR, C¹³ NMR, Mass spectra and ¹H NMR. The compounds were assessed for their in-vitro antimicrobial activity with pathogenic microbe comprising Gram positive bacterial strains, *S. aureus* and Gram negative strains *E.coli*, *P.vulgaris*, and *S. typhi* at different concentration. The consequence of bioassay is compared with standard drug Chloramphenicol.

Keywords: indazol, ceric (IV) ammonium nitrate catalyst, ultrasound irradiation, ecofriendly media, antimicrobial screening

1. Introduction

Indazole was first defined as a “pyrazole ring fused with the benzene ring” by the scientist Emil Fisher. It is broadly studied due to its remarkable chemical and biological properties. Indazole is from the azoles family containing carbon, hydrogen and nitrogen atoms. Indazole also called as benzpyrazole or isoindazolone which containing two nitrogen atoms. It is ten π -electron aromatic heterocyclic systems as a pyrazole molecule. The structure of indazole is given below in cylindrical bonds is as (**Figure 1**).

Indazole derivatives are pharmacologically significant as they form the fundamental structure of numerous drug molecules, like Benzydamine used as anti-inflammatory agent and Granisetron, 5HT₃ receptor antagonist for anti-emetic in cancer chemotherapy. Two nitrogen atoms in indazole can be able to be functionalized with high selectivity at different positions. Indazole show a range of biological activity such as anti-HIV, anti-cancer, anti-platelet, anti-inflammatory, serotonin 5-HT₃ receptor antagonist and anti-tumouractivities [1–6]. 3-Aminoindazoles which are valuable templates for medicinal chemistry. The scaffold is found in a huge number of compounds exhibiting a large number of biological activities including kinase inhibitors, HIV protease inhibitors, MCH

Figure 1.
Naturally accruing indazole nucleus.

receptor1 antagonists, CB1 receptor inhibitors and factor XIa inhibitors [7–9]. The 3-aminoindazoles have been able to mimic the adenine nucleus of ATP for the design of ATP-competitive receptor tyrosine kinase inhibitors with potent antitumor activities. Thus it is been potential valuable templates for pharmaceutical chemistry, hence effort has recently been taken to the synthesis of substituted indazole. Several method have been published for the synthesis of 3-aminoindazole the methods have several drawback is the use of costly reagents and catalyst, organic solvents, harsh conditions and thus have limited scope [10–13]. In last few decades Chemist have attraction for Nitrogen containing heterocycle which possess potential antimicrobial property [14–16]. Indazole can be present in two forms which result from the displacement of proton among two nitrogen atoms, a method describe as proto tropic annular tautomerism. Without substituted indazole be present mostly as the 1H-tautomer based on the results from molecular studies.

The indazole ring contains two nitrogen atoms and thus annular tautomerism with concern to the location of the NH hydrogen atom. The variation in energy among tautomer's the benzenoid type predominates in the gas phase solution. Solid state derivatives are generally found thermodynamically more constant than the analogous 2H forms, annular tautomerism of indazole benzenoid 1H-indazole tautomer and quinonoid 2H-indazole tautomer. Ortho-hydrazine benzoic acid on heating results in the formation of indazolone reported by Emil Fisher in 1800 (Figure 2) [17–20].

Biological importance of 3-aminoindazole Derivatives:- Indazoles are naturally occurring alkaloids like Nigellidine, Nigellicine and Nigeglanine. Nigellicine was isolated from extensively spread plant *Nigella sativa*. Nigeglanine was isolated from extracts of *Nigella glandulifera*. Merely few of the alkaloids studied upon isolation show the presence of indazole ring system. The first member of this alkaloid family Nigellicine [21] which is isolated in 1985 from the plant *N. sativa* an annual flowering plant, native to Southwest Asia. The seeds of this plant are used for thousands of years as a spice and for the treatment of a variety of diseases [22–24]. The structure of nigellicine has an intramolecular hydrogen bond among the carboxylate oxygen atom and the hydroxyl group. The structure of nigellicine is a pseudo cross conjugated heterocyclic mesomerichbetaine, which means that it be able to be presented by dipolar canonical formula where both the positive and negative charge is delocalized in the structure [25].

Similarly other two alkaloids (Figure 3) Nigeglanine and Nigellidine are isolated from extracts of *N. glandulifera* and *N. sativa*. These two compounds be able to also be obtainable by their zwitterions formulae [26]. Indazole core is present in naturally occurring alkaloids and biologically active molecules. Nigellidine is a natural product containing an indazole nucleus, isolated from plant *N. sativa* and used in the treatment of a variety of diseases. Indazole and their derivatives are found to have a large range of activities. Previous findings on indazole derivatives are purposely known to be active as protein kinase inhibitors, cancer cell proliferative

Annular prototropic tautomerism of indazole

First reported synthesis of indazolone

Figure 2.
Naturally accruing indazole nucleus.

Figure 3.
Naturally accruing indazole nucleus.

disorders, the methods 3-aminoindazole have several drawback is the use of costly reagents and catalyst, organic solvents, harsh conditions and thus have limited scope [27, 28].

Stimulated from these observation and literature exploration revealed that no green and efficient, method is reported yet hence in the present work we are endeavored to synthesize 3-aminoindazole by using ultrasonic radiation and ceric ammonium nitrate (CAN) $[\text{Ce IV}(\text{NO}_3)_6]_2$ as a catalyze reactions in organic synthesis because of many advantages such as good solubility in water, easily available, non-toxicity, simple work-up procedure, low cost, high reactivity and synthesized substituted-1H-indazol-3-amine derivative (3a-h) and screened for their antimicrobial activity [29–34].

2. Material and methods

Chemicals used for the synthesis were of AR grade of Merck, S.D. Fine and Aldrich. The reactions were examined by E. Merck TLC aluminum sheet silica

gel60F254 and visualizing the spot in UV Cabinet and iodine chamber. The melting points were note down in open capillary in paraffin bath and are uncorrected. ^1H NMR spectra are logged on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO- d_6 as solvent. Chemical Shifts are specified in parts per million (ppm). Positive-ion Electro Spray Ionization (ESI) mass spectra were acquired with a Waters Micromass Q-TOF Micro, Mass Spectrophotometer. IR spectra were recorded on a Shimadzu IR Spectrophotometer (KBr, ν_{max} in cm^{-1}). The compounds are purified by using column chromatography on silica gel (60–120 mesh). Elemental (CHN) examination was done using Thermo Scientific (Flash-2000), the compounds were investigated for carbon, hydrogen and nitrogen and the results found are in good agreement with the calculated values.

3. Experimental section

3.1 The optimization of the reaction conditions

The optimization of the reaction is done using different solvents and also solvent free condition was applied and the reaction carried out under ultrasound irradiation. When the reaction was performed without solvent the yield obtained was in trace amount. When different solvent like acetonitrile, toluene and ethanol it the yield was less and the time taken for completion of reaction was more. But using (CAN) (10 mol %) EtOH- H_2O (2:2) (entry 9) at 50–60°C for 35 min. we got good yield in less time and thus the reaction was optimized. The results were summarized in (Table 1).

General Procedure for the synthesis 3-aminoindazole (3a-h):- A mixture of benzonitrile (**1a-h**) (1.0 mmol), hydrazine (**2a-h**) (1.2 mmol) and (CAN) (10 mol) in solvent EtOH- H_2O (2:2) were taken in single neck round bottom flask and the flask containing reaction mixture was kept in the ultrasonic bath and was irradiated at 50–60°C for about 30–40 min. (the progress of reaction was monitored by TLC at different interval) separately as indicated in (Table 2). After the reaction was completed the reaction mass was poured on crushed ice. The obtained solid was

Entry	CAN mol (%)	Solvent	Time (min)	Yield (%)
1	—	—	80	5
2	5	MeCN	60	40
3	10	MeCN	60	58
4	5	Toluene	70	53
5	10	Toluene	70	60
6	5	EtOH	60	68
7	10	EtOH	60	76
8	5	EtOH- H_2O (2:2)	35	80
9	10	EtOH- H_2O (2:2)	35	93
10	15	EtOH- H_2O (2:2)	35	86

Table 1.
Optimizing of the reaction conditions for 5-bromo-1-methyl-1H-indazol-3-amine (**3c**).

Comp.	R	R'	product	m.p (°C)	Yield (%)
3a	H	Me		95–97	90
3b	H	H		150–152	87
3c	5-Br	Me		133–135	93
3d	5-Cl	Me		130–132	89
3e	6-OMe	H		116–120	90
3f	4-Br	H		171–174	95
3g	5-I	H		177–179	93
3h	5-F	H		165–167	90

Table 2.
CAN catalyze synthesis of 3-aminoindazole under ultrasound irradiation (3a–3 h).

filtered, washed with water and dried. The crude compound was crystallized using DMF-Ethanol. Their structure was confirmed by ^1H NMR, physical data, mass, IR and elemental analysis.

1-methyl-1H-indazol-3-amine (3a):

IR (KBr, ν_{max} in cm^{-1}): 3422 (N-H str., -Amine), 2982, 2942 (C-H asym. Str. aliphatic), 2830 (C-H sym. Str., aliphatic), 3054 (C-H str., aromatic), 1540 (C=N str., Indazolyl), 1342 (C-N str.), 1504, 1465 (C=C str., aromatic), 1119, 1126 (C-H i. p. def., aromatic), 867 (C-H o.o.p. def., aromatic).

^1H NMR δ ppm (DMSO- d_6): δ 3.79 (s, 3H, $-\text{CH}_3$), 5.36 (s, 2H, Amine), 7.2–7.8 (m, 4H, Ar-H).

^{13}C -NMR (100 MHz, DMSO): δ 35.52, 110.06, 112.34, 118.15, 122.83, 128.64, 139.45, 147.50 ppm.

LCMS (ESI+) m/z : 148 $[\text{M} + 1]^+$, 271 $[\text{M} + \text{Na}]^+$, 249 $[\text{M} + \text{Na} + \text{H}]^+$.

Elemental Analysis: Calcd. For $\text{C}_8\text{H}_9\text{N}_3$; calculated: C, 65.29; H, 6.16; N, 28.55
Found: C, 64.54; H, 6.19; N, 27.95.

General Reaction:- Synthesis of compounds Indazole (3a-3 h) Derivatives.

Where, R = H, Br, Cl, OMe, I, F.

R' = Me, H

1-H-Indazol-3-amine (3b):

IR (KBr, $\nu_{\max}$ in cm^{-1}): 3420 (N-H str., -Amine), 2980, 2941 (C-H asym. str. aliphatic), 2833 (C-H sym. Str., aliphatic), 3051 (C-H str., aromatic), 1544 (C=N str., Indazolyl), 1343 (C-N str.), 1503, 1464 (C=C str., aromatic), 1116, 1123 (C-H i. p. def., aromatic), 864 (C-H o.o.p. def., aromatic), 554 (C-Br str., Ar-Br).

^1H NMR δ ppm (DMSO- d_6): 5.41 (s, 2H, -NH₂), 12.4 (s, 1H, ring-N-H), 7.2–7.7 (m, 4H, Ar-H).

^{13}C NMR δ ppm (DMSO- d_6): δ 41.55, 108.01, 113.34, 117.75, 126.88, 128.62, 141.59,

LCMS (ESI+) m/z : 134[M + 1]⁺, 157[M + Na]⁺, 158[M + Na + H]⁺.

Elemental Analysis: Calcd. For C₇H₇N₃; calculated: C, 63.14; H, 5.30; N, 31.56 Found: C, 63.17; H, 5.34; N, 31.34.

5-bromo-1-methyl-1H-indazol-3-amine (3c):

IR (KBr, $\nu_{\max}$ in cm^{-1}): 3424 (N-H str., -Amine), 2983, 2943 (C-H asym. Str. aliphatic), 2834 (C-H sym. Str., aliphatic), 3052 (C-H str., aromatic), 1541 (C=N str., Indazolyl), 1344 (C-N str.), 1501, 1464 (C=C str., aromatic), 1116, 1122 (C-H i. p. def., aromatic), 861 (C-H o.o.p. def., aromatic), 556 (C-Br str., Ar-Br).

^1H NMR δ ppm (DMSO- d_6): 3.65 (s, 3H, -CH₃), 5.47 (s, 2H, -NH₂), 7.5–7.6 (d, 2H, Ar-H), 7.93 (s, 1H, Ar-H).

^{13}C NMR δ ppm (DMSO- d_6): 34.55, 109.01, 110.34, 115.75, 122.88, 128.62, 139.59, 147.69.

LCMS (ESI+) m/z : 225[M + 1]⁺, 248[M + Na]⁺, 249[M + Na + H]⁺.

Elemental Analysis: Calcd. For C₈H₈BrN₃; calculated: C, 42.50; H, 3.57; Br, 35.34; N, 18.59 Found: C, 42.45; H, 3.59; N, 18.62.

5-chloro-1-methyl-1H-indazol-3-amine (3d):

IR (KBr, $\nu_{\max}$ in cm^{-1}): 3423 (N-H str., -Amine), 2976, 2943 (C-H asym. Str. aliphatic), 2834 (C-H sym. Str., aliphatic), 3053 (C-H str., aromatic), 1541 (C=N str., Indazolyl), 1345 (C-N str.), 1501, 1462 (C=C str., aromatic), 1114, 1122 (C-H i. p. def., aromatic), 863 (C-H o.o.p. def., aromatic), 554 (C-Br str., Ar-Br).

^1H NMR δ ppm (DMSO- d_6): δ 3.81 (s, 3H, -CH₃), 5.36 (s, 2H, -NH₂), 7.3–7.5 (d, 2H, Ar-H), 7.85 (s, 1H, Ar-H).

^{13}C NMR δ ppm (DMSO- d_6): δ 35.41, 110.03, 114.34, 120.75, 125.88, 126.62, 136.59, 146.61.

LCMS (ESI+) m/z : 182[M + 1]⁺, 205[M + Na]⁺, 206[M + Na + H]⁺.

Elemental Anal. Calcd. For C₈H₈ClN₃; calculated: C, 52.90; H, 4.44; N, 23.14 Found: C, 52.93; H, 4.40; N, 23.15.

4-methoxy-1H-indazol-3-amine (3e):

IR (KBr, $\nu_{\max}$ in cm^{-1}): 3426 (N-H str., -Amine), 2983, 2943 (C-H asym. Str. aliphatic), 2834 (C-H sym. Str., aliphatic), 3053 (C-H str., aromatic), 1542 (C=N

str., Indazolyl), 1346 (C-N str.), 1506,1460 (C=C str., aromatic), 1113, 1120 (C-H i. p. def., aromatic), 865 (C-H o.o.p. def., aromatic), 553 (C-Br str., Ar-Br).

¹H NMR δ ppm (DMSO-*d*₆): δ 3.73 (s, 3H, -CH₃), 5.43 (s, 2H, -NH₂), 6.7 (d, 1H, Ar-H), 7.2 (d, 1H, Ar-H), 7.5 (d, 1H, Ar-H), 12.4 (s, 1H, -NH of ring).

¹³C-NMR δ ppm (DMSO-*d*₆): δ 55.09, 95.02, 105.8, 106.8, 127.04, 142.02, 149.05, and 153.12.

LCMS (ESI+) *m/z*: 164[M + 1]⁺, 187 [M + Na]⁺, 188[M + Na + H]⁺.

Elemental Anal. Calcd. For C₈H₉N₃O; calculated: C, 58.88; H, 5.56; N, 25.75
Found: C, 58.30; H, 5.43; N, 25.70.

6-bromo-1H-indazol-3-amine (3f):

IR (KBr, $\nu_{\max}$ in cm⁻¹): 3421 (N-H str., -Amine), 2984, 2944 (C-H asym. Str. aliphatic), 2835 (C-H sym. Str., aliphatic), 3052 (C-H str., aromatic), 1541 (C=N str., Indazolyl), 1347 (C-N str.), 1504,1466 (C=C str., aromatic), 1117, 1125 (C-H i. p. def., aromatic), 866 (C-H o.o.p. def., aromatic), 553 (C-Br str., Ar-Br).

¹H NMR δ ppm (DMSO-*d*₆): 5.38 (s, 2H, -NH₂), 7.4(d, 1H, Ar-H), 7.7(d, 1H, Ar-H), 7.8 (s, 1H, Ar-H), 12.4 (s, 1H, ring-N-H).

¹³C-NMR δ ppm (DMSO-*d*₆): 107.04, 113.34, 120.05, 122.03, 124.22, 143.10, 149.32. **LCMS (ESI+) *m/z*:** 212[M + 1]⁺, 235[M + Na]⁺, 236[M + Na + H]⁺.

Elemental Anal. Calcd. For C₇H₆BrN₃; calculated: C, 39.65; H, 2.85; N, 19.82
Found: C, 39.62; H, 2.82; N, 19.78.

5-iodo-1H-indazol-3-amine (3 g):

IR (KBr, $\nu_{\max}$ in cm⁻¹): 3419 (N-H str., -Amine), 2984, 2945 (C-H asym. Str. aliphatic), 2836 (C-H sym. Str., aliphatic), 3055 (C-H str., aromatic), 1541 (C=N str., Indazolyl), 1343 (C-N str.), 1505,1467 (C=C str., aromatic), 1120, 1125 (C-H i. p. def., aromatic), 861 (C-H o.o.p. def., aromatic), 556 (C-Br str., Ar-Br).

¹H NMR δ ppm (DMSO-*d*₆): 5.44 (s, 2H, -NH₂), 7.4(d, 1H, Ar-H), 7.7(d, 1H, Ar-H), 8.2 (s, 1H, Ar-H), 12.4 (s, 1H, ring -N-H).

¹³C-NMR δ ppm (DMSO-*d*₆): 88.3, 110.18, 115.37, 129.15, 134.23, 128.62, 140.31, 149.81 **LCMS (ESI+) *m/z*:** 259[M + 1]⁺, 282[M + Na]⁺, 283[M + Na + H]⁺.

Elemental Anal. Calcd. For C₇H₆IN₃; calculated: C, 32.46; H, 2.33; N, 16.22
Found: C, 32.35; H, 2.36; N, 15.98.

5-fluoro-1H-indazol-3-amine (3 h):

IR (KBr, $\nu_{\max}$ in cm⁻¹): 3425 (N-H str., -Amine), 2983, 2943 (C-H asym. Str. aliphatic), 2835 (C-H sym. Str., aliphatic), 3056 (C-H str., aromatic), 1546 (C=N str., Indazolyl), 1347 (C-N str.), 1502,1465 (C=C str., aromatic), 1119, 1126 (C-H i. p. def., aromatic), 865 (C-H o.o.p. def., aromatic), 556 (C-Br str., Ar-Br).

¹H NMR δ ppm (DMSO-*d*₆): 4.98 (s, 2H, -NH₂), 7.1(d, 1H, Ar-H), 7.6(d, 1H, Ar-H), 7.9 (s, 1H, Ar-H), 12.41 (s, 1H, ring -N-H).

¹³C-NMR δ ppm (DMSO-*d*₆): 107.12, 110, 112.17, 115.17, 134.23, 149.81, 153.32.

LCMS (ESI+) *m/z*: 259[M + 1]⁺, 282[M + Na]⁺, 283 [M + Na + H]⁺.

Elemental Anal. Calcd. For C₇H₆FN₃; calculated: C, 55.63; H, 4.00; N, 27.80
Found: C, 55.67; H, 3.98; N, 27.40.

3.2 Physico-chemical characterization

Benzonitrile (**1a-h**) is reacted with hydrazine (**2a-h**) in presence of catalyst ceric (IV) ammonium nitrate (CAN) in solvent EtOH-H₂O by using ultrasonic irradiation which undergoes cyclocondensation reaction to give substituted 3-aminoindazole (**3a-h**). The physical constants like melting point and solubility were determined for all the intermediate and final products. At every stage the reaction is monitored with TLC. Newly synthesized compound have been characterized on the basis of spectral data and elemental analysis such as FT-IR, ¹H NMR, ¹³CNMR and mass spectra and they also screened for antimicrobial activities.

The IR spectrum of **3c** showed strong band absorption bands at 3424 cm⁻¹ due to -NH- stretch in amine while bands at 1541 cm⁻¹ is observed due to C=N stretch in Indazolyl and absorption band at 556 cm⁻¹ shows C-Br aromatic stretching and stretch at 1344 cm⁻¹ was observed for C-N str group confirms the cyclisation to form 5-bromo-1-methyl-1H-indazol-3-amine**3c**. ¹H NMR of **3c** revealed a singlet signal at 3.65 ppm, at aliphatic region owing to three protons of -CH₃ group attached to aromatic ring, one more singlet at δ 5.47 ppm confirm protons of

Compd. Code	Zone of Inhibition (mm)											
	Gram + ve						Gram -ve					
	<i>S. aureus</i>						<i>P. vulgaris</i>					
	Conc. (µg/mL)						Conc. (µg/mL)					
	1000	500	250	125	63.5	31	1000	500	250	125	63.5	31
3a	21	22	21	20	17	13	27	24	21	18	17	10
3b	23	21	20	18	16	18	25	22	19	16	14	09
3c	25	21	19	20	16	15	28	23	21	17	15	11
3d	23	22	21	19	18	15	27	24	20	18	17	12
3e	19	20	16	15	13	14	21	19	15	14	13	09
3f	24	23	21	20	17	16	25	23	21	19	15	08
3 g	23	20	18	17	16	13	23	22	21	16	14	10
3 h	20	18	16	15	13	11	26	21	17	15	12	09
DMSO	—	—	—	—	—	—	—	—	—	—	—	—
Std. Drug Chloramphenicol	25	22	20	19	17	15	26	24	23	21	17	15

Table 3. Antibacterial profile of 3-aminoindazole derivative (3a-h) .

Compd. Code	Zone of Inhibition (mm)											
	Gram -ve											
	<i>E. coli</i>						<i>S. typhi</i>					
	Conc. (µg/mL)						Conc. (µg/mL)					
	1000	500	250	125	63.5	31	1000	500	250	125	63.5	31
3a	26	24	22	21	16	12	16	15	12	11	10	09
3b	24	21	19	18	17	16	16	14	10	09	06	07
3c	25	24	20	17	16	15	17	16	11	10	09	08
3d	26	23	21	20	17	11	14	10	08	08	07	09
3e	23	22	20	18	14	12	16	14	12	11	09	07
3f	25	24	22	20	18	15	17	16	11	10	09	08
3 g	21	20	17	16	14	11	15	13	11	10	08	07
3 h	22	21	20	18	16	13	14	12	10	08	06	05
DMSO	—	—	—	—	—	—	—	—	—	—	—	—
Std. Drug Chloramphenicol	26	24	23	21	17	14	17	15	12	11	09	08

Table 4. Antibacterial profile of 3-aminoindazole derivative (3a-h).

-NH₂- group, Remaining ¹H NMR signal is present at aromatic region as expected. C¹³ NMR also supported data singlet signal at δ34.55, ppm revealed one aliphatic carbon, of -CH₃ attached to indazole ring. ESI-MS Mass spectra also confirm the molecular ion at (m/z) value at 225[M + 1]⁺, and further supported by elemental analysis data found to be in good agreement with the molecular formula of C₈H₈BrN₃.

Potent antibacterial/inhibition profile of 3-amino indazole (at different concentration) by agar disc-diffusion method: - The entire novel synthesized heterocyclic compounds **3a-h** was screened for their *in-vitro* antimicrobial activity using disc-diffusion method. Their activity was compared with well-known commercial antibiotic Chloramphenicol. Antibacterial activity was determined by using Mueller Hinton Agar obtained from Hi media Ltd., Mumbai. Petri plates were prepared by pouring 10 mL of Mueller Hinton Agar for bacteria containing micro-
bial culture was allowed to solidify. Test solutions were prepared with known weight of compound in DMSO and half diluted suitably to give the resultant

Figure 4.
Antimicrobial activity of compound 3a-h against Gram - bacteria S. aureus and P. vulgaris.

concentration of 31-1000 µg/mL. Whatmann no.1 sterile filter paper discs (6 mm) were impregnated with solution and allowed to dry at room temperature. The discs were then applied and the plates were incubated at 37°C for 24 h (bacteria) and the inhibition zone (Figure 6) was measured as diameter in four directions and expressed as mean. The results of the antimicrobial screening are illustrated in the Tables 3 and 4. From the results it is clear that the compounds tested showed variable toxicity against different bacteria.

3.3 Mechanism of inhibition/prohibition

Gram-negative bacteria habitually owe low susceptibility as outer membrane of their cell wall not gets blocked/penetrated by drugs easily and factors like amount of peptidoglycan, receptors, and lipids availability, nature of cross-linking, autolytic enzymes activity greatly influence the bio-activity, permeation, and incorporation of the antibacterial drugs. There are three behaviors in which antibacterial drugs have thus far been shown to exert their definite actions upon bacteria: 1) by interfering with the synthesis of the relatively rigid cell wall which

Figure 5. Antimicrobial activity of compound 3a-h against Gram - bacteria E. coli and S. typhi.

Figure 6.
Zone of inhibition in mm.

Maintains the structural integrity of the bacterial cell (2) by destructivethe elusive membrane, which encompasses the bacterial cytoplasm and assists as an essential osmotic barricade to the free diffusion of severalmetabolites and (3) by blocking cytoplasmic metabolic reactions which are involved in critical synthetic processes within the cell. Consequences of bioassay indicated that compound (**Figures 4 and 5**) **3a, 3c, 3d, 3f** showed excellent activity against *S. aureus* and *P.vulgaris* and *E.coli*. Remaining compounds exhibited reasonable activity against selected bacterial strains.

4. Conclusions

In summary, in the present chapter we have described an efficient simple and reproducible method afforded various amino indazole derivatives (**3a-h**) in excellent yields, and without formation of undesirable side products. The synthetic protocol has been outlined in general reaction. At every stage the reaction was monitored with TLC. The physical constants like melting point and solubility were determined for all the intermediate and final products. Newly synthesized compound has been characterized on the basis of spectral data and elemental analysis such as FT-IR, ^1H NMR, ^{13}C NMR and mass spectra this chapter focused on helping futuristic researchers, clinicians, and academicians involved in synthesizing and corresponding biological screening of innate activity of certain novel amino indazole heterocycleswe have described here novel series of Indazole (**3a-h**) derivative. The presented series of compounds were synthesized in decent yields. The structure and purity of newly synthesized compounds were established by spectroscopic investigation and chemical examination. Antibacterial screening of synthesized substituted indazole (**3a-h**) derivatives exhibited a potent bactericidal. Thus, it could be powerfully stimulates major advances in remarkable significant chemotherapeutics in medicine, biology and pharmacy. Overall these indazole disturb

macromolecules like cytoplasmic membrane covering cytoplasm which acts selective barrier to control internal composition of cell. Amino indazole derivative particularly interrupted such functional roles of cytoplasmic membrane and ionic outflow that resulted cell destruction/death. Synthesized potent bioactive substituted indazole derivatives may open new possibilities in the successful treatment of several diseases due to promising antibacterial profile. So, ample scope exists in further research of this heterocycle especially innate selectivity of these compounds needs to carry out their chemotherapy as potent antibacterial aims to target cell membrane of range of Gram-negative bacteria as to derive novel drugs of Inventive era. Among the synthesized compounds most of the compounds exhibited good to moderate activity against selected strains *S. aureus*, *P. vulgaris* and *E. coli* while poor activity was evaluated for *S. typhi* (**Figure 5**). This variation in toxicity it may attribute due to union of different substituent attached to the core 3-aminoindazole which may enhances the biological activities of parent nucleus.

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Conflict of interest

The authors declare no conflict of interest.

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