Design, Synthesis, Characterization, and Antimicrobial Screening of Novel Indazole Bearing Oxadiazole Derivatives

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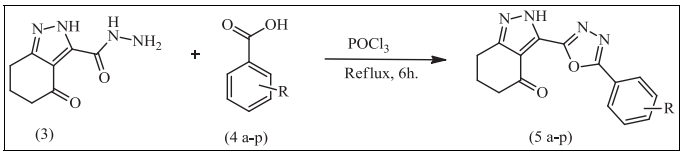
Received June 1, 2015
DOI 10.1002/jhet.2540
Published online in 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



Ethyl 2-(2,6-dioxocyclohexyl)-2-oxoacetate was prepared by reacting cyclohexane-1,3-dione (**1**) and diethyl oxalate (**2**) with the help of sodium ethoxide in ethanol at 0–5°C. Subsequent treatment of ethyl 2-(2,6-dioxocyclohexyl)-2-oxoacetate with hydrazine hydrate in ethanol resulted into ethyl 4-oxo-4,5,6,7-tetrahydro-2*H*-indazole-3-carboxylate while without solvent in excess hydrazine hydrate on reflux resulted into 4-oxo-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (**3**). The synthesis of novel indazole bearing oxadiazole derivatives (ODZ 01 to 16) has been achieved by the reaction of hydrazide of 2*H*-indazole (**3**) with acid (**4a–p**) in the presence of $POCl_3$, and the antimicrobial activity of synthesized novel compounds has been studied.

J. Heterocyclic Chem., **00,** 00 (2016).

INTRODUCTION

The systematic IUPAC name benzo[*c*]pyrazole is not used in the *ring index* or in *chemical abstract*, and the heterocycle is normally referred to its trivial name indazole or more correctly 1*H*-indazole (CAS registry number 271-244-3). Alternative names for indazole, such as 1,2-benzodiazole, are not used. Benzo-fused derivatives are known as benzopyrazoles (Fig. 1). The first indazoles were synthesized in 1880 [1], and a systematic investigation of the heterocycle was performed by V. Auwers in 1924 [2]. Indeed, general synthetic pathways to indazoles were developed in the early years of the 20th century, and many recent publications describe improvements of known methods. Methods for the synthesis of indazoles are described in *Houben-Weyl* [3], and well-tested procedures for the synthesis of 1*H*-indazole [4–7], 2-phenyl-2*H*-indazole [8], and 5-nitro-1*H*-indazole [9] can be found in *Organic Synthesis*.

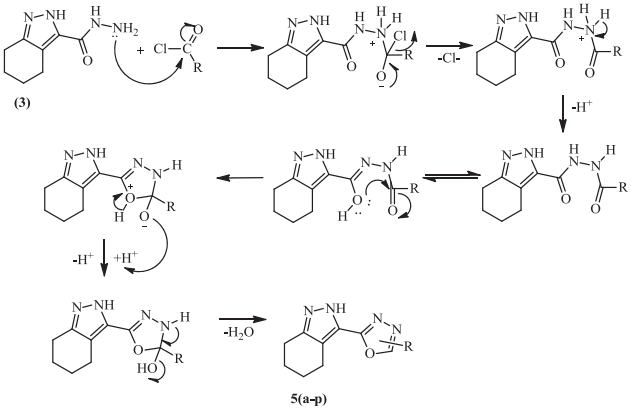
Natural products bearing an indazole structure are rare [10], and at present only, two examples are known: nigellicine [11] and nigellidine [12]. However, many synthetic indazoles are known, and a number are important because of their pharmaceutical activity; some act as dopamine antagonists, anti-inflammatory, and analgesic or antipyretic agents [13–20]. Others also exhibit CNS activity [21–23], and 6-nitroindazoles and 7-nitroindazoles are used to study the behavior of nitric oxide *in vivo* [24–26]. 1-Benzyl-1*H*-indazole-3-carboxilic acids have antispermatogenetic and anticancer activity [27–29], the latter effect being shared by other indazole derivatives [30–32]. 1-Benzoyl-1*H*-indazoles behave as anti-arthritic drugs [33], and 4-nitro- and 4-amino-2-ribofuranosyl-2*H*-indazole 3′,5′-cyclic monophosphates act as potent mimics of adenosine-3′,5′-cyclic monophosphates [34]. Cortivazol [35] is an indazole-based drug possessing glucocorticoid properties. Many indazoles act as enzyme inhibitors [36–38], and some also show specific virucide [39], bronchodilatory [40–42], vasodilatory [43], or neuroprotectant [44] activities; others are used in the treatment of diabetes [45]. 3-Trifluoromethyl-1*H*-indazoles possess trichomonacide properties [46], and fused indazoles with an azasteroid ring system show antimicrobial activity [47]. Some 1*H*-indazole-4,7-quinones possess anthelmintic [48] and diuretic activity [49]. A series of indazole derivatives exhibit herbicide activity, behave as growth inhibitors [50–52], or are used as bactericides and fungicides in polymer-based paints [53]. Guanidino-1*H*-indazoles are used as sweeteners [54].

Although many derivatives of indazole show biological activity, no special toxicity has been reported, and no special handling precautions have been recommended. The biodegradability of indazole is included in an ecological survey of heterocyclic compounds [55].

1,3,4-Oxadiazole (**1**) is a thermally stable aromatic heterocycle and exists in two partially reduced forms: 2,3-dihydro-1,3,4-oxadiazole(1,3,4-oxadiazoline) (**2**) and 2,5-dihydro-1,3,4-oxadiazole(1,3,4-oxadiazoline) (**3**), depending on the position of the double bond. The completely reduced form of the 1,3,4-oxadiazole is known as 2,3,4,5-tetrahydro-1,3,4-oxadiazole (1,3,4-oxadiazolidine) (**4**) [56] (Fig. 2).

RESULTS AND DISCUSSION

The following is the possible reaction mechanism for compound (**3**) to (**5a–p**) (Table 1).



Possible Reaction Mechanism for Compound (3) to (5a-p)

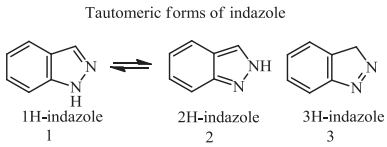


Figure 1. Tautomeric forms of indazole.

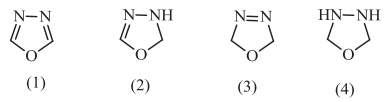


Figure 2. Dihydro forms of 1,3,4-oxadiazolidine.

CONCLUSION

The results from in vitro antibacterial screening of all synthesized compounds against *S. aurues* MTCC-96 and *B. subtillitis* MTCC-441 were very much encouraging than antifungal screening against *A. niger* MTCC-282 and *C. albicans* MTCC-227. The result shows that the compounds **02**, **10**, **12**, **13**, and **16** exhibited significant (maximum) antibacterial activities, while other compounds show moderate to low activity. All of the synthesized compounds are given lower antifungal activity. On evaluation of antibacterial screening data, it can be seen that the extent of zone of inhibition is largely affected by the type of substitutions at phenyl ring, irrespective of the positions of substitution. Electron-withdrawing group at phenyl ring considerably enhanced the antibacterial activity, whereas electron-releasing groups on phenyl ring strongly diminished the antibacterial activity, which can be evident by antibacterial screening results. Further investigations in the area of novel indazole bearing oxadiazole derivatives incorporated with different substituent are in progress in our laboratory.

EXPERIMENTAL

Synthesis of 4-oxo-4,5,6,7-tetrahydro-2H-indazole-3-carbohydrazide (3). To the stirred solution of sodium ethoxide (0.2 mol), a mixture of cyclohexane-1,3-dione (**1**) (0.2 mol) and diethyl oxalate (**2**) (0.2 mol) was added dropwise below 5–10°C. Vigorous stirring was required to prevent complete solidification of the reaction mixture. After completion of the reaction, the reaction mixture was decomposed by the careful addition of cold dilute sulfuric acid solution. The ethyl 2-(2,6-dioxocyclohexyl)-2-oxoacetate separated as heavy oil. Ethyl 2-(2,6-dioxocyclohexyl)-2-oxoacetate is added into access 80% hydrazine hydrate and refluxed for 5 to 6 h. The reaction mixture was allowed to cool at room temperature, and the precipitate obtained was filtered, dried and recrystallized from ethanol to give analytical pure product in 85% yield.

Table 1

Synthesis of substituted oxadiazole and triazole derivatives.

Entry	Code	R	Molecular formula	Molecular weight	Yield (%)	MP (°C)
5a	ODZ 01	4-CH_3	$C_{16}H_{14}N_4O_2$	294	90	180–182
5b	ODZ 02	4-OCH_3	$C_{16}H_{14}N_4O_3$	310	91	176–178
5c	ODZ 03	-H	$C_{15}H_{12}N_4O_2$	280	84	186–188
5d	ODZ 04	2-CH_3	$C_{16}H_{14}N_4O_2$	292	90	192–194
5e	ODZ 05	4-Cl	$C_{15}H_{11}ClN_4O_2$	314	86	187–189
5f	ODZ 06	4-Br	$C_{15}H_{11}BrN_4O_2$	358	90	183–185
5g	ODZ 07	4-F	$C_{15}H_{11}FN_4O_2$	298	90	195–197
5h	ODZ 08	4-OH	$C_{15}H_{12}N_4O_3$	296	86	188–190
5i	ODZ 09	3-Cl	$C_{15}H_{11}ClN_4O_2$	314	89	185–187
5j	ODZ 10	3-Br	$C_{15}H_{11}BrN_4O_2$	358	89	195–197
5k	ODZ 11	2-Cl	$C_{15}H_{11}ClN_4O_2$	314	88	201–203
5l	ODZ 12	2-NO_2	$C_{15}H_{11}N_5O_4$	325	90	178–180
5m	ODZ 13	2,5-di-OMe	$C_{17}H_{16}N_4O_4$	340	90	183–185
5n	ODZ 14	3,4-di-OMe	$C_{17}H_{16}N_4O_4$	340	87	186–188
5o	ODZ 15	4-NO_2	$C_{15}H_{11}N_5O_4$	325	85	195–197
5p	ODZ 16	2-Br	$C_{15}H_{11}BrN_4O_2$	358	90	238–240

MP, melting point

Yellowish white solid; R_f 0.37 (6:4 hexane-EtOAc); IR (KBr) ν: 3280, 3140, 3078, 2941, 2862, 1680, 1668, 1579, 1467, 1259, 1024, 742 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 2.15 (m, 2H, CH_2), 2.68 (t, 2H, CH_2), 2.82 (t, 2H, CH_2), 4.58 (s, 2H, $-NH_2$), 9.82 (s, 1H, −NH), 13.12 ppm (s, 1H, −NH); ^{13}C NMR (400 MHz, DMSO): δ 20.1, 24.2, 38.8, 121.5, 142.6, 153.8, 162.2, 197.2 ppm; MS: *m/z* 194 (M^+). *Anal*. Calcd. for $C_{16}H_{14}N_4O_2$: C, 49.48; H, 5.19; N, 28.85; O, 16.48. Found: C, 49.56; H, 5.21; N, 28.91; O, 16.42.

General procedure for the synthesis of 3-(5-aryl-1,3,4-oxadiazol-2-yl)-6,7-dihydro-2H-indazol-4(5H)-one (5a–p) [ODZ 01 to 16]. Equimolar amount of 4-oxo-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (**3**) and appropriate carboxylic acid (**4a–p**) were taken in $POCl_3$. The reaction mixture is refluxed for 6 h, allowed to cool at room temperature, poured into crushed ice, and stood by overnight. The solid was filtered, dried, and recrystallized from ethanol to give analytical pure product in 85–90% yield.

Spectral data of the synthesized compounds [ODZ 01 to 16].

3-(5-(p-tolyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Creamish solid; R_f 0.33 (6:4 hexane-EtOAc); IR (KBr) ν: 3186, 3149, 3078, 3012, 2941, 2862, 1752, 1668, 1579,1467, 1249, 1014, 819, 777, 742 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 1.80 (m, 2H, CH_2), 2.39 (s, 3H, $-CH_3$), 2.69 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 7.25–7.27 (dd, 2H, Ar-H, $^3J = 8.4$ Hz), 7.93–7.95 (dd, 2H, Ar-H, $^3J = 8.4$ Hz), 10.58 ppm (s, 1H, −NH-); ^{13}C NMR (400 MHz, DMSO): δ 21.22, 21.44, 21.67, 22.36, 22.82, 117.22, 120.92, 126.84, 126.95, 129.71, 129.77, 133.15, 142.24, 142.46, 160.13, 163.93 ppm; MS: *m/z* 294 (M^+). *Anal*. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04; O, 10.87. Found: C, 65.41; H, 4.69; N, 19.08; O, 10.91.

3-(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Creamish solid; R_f 0.35 (6:4 hexane-EtOAc); IR (KBr) ν: 3394, 3115, 3068, 2939, 2850, 1763, 1597, 1566, 1458, 1253, 1168, 1126, 1024, 831, 723, 680 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 1.82 (m, 2H, CH_2), 2.71 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.58 (s, 3H, $-CH_3$), 7.19–7.21 (dd, 2H, Ar-H, $^3J = 8.4$ Hz), 7.90–7.92 (dd, 2H, Ar-H, $^3J = 8.4$ Hz), 10.62 ppm (s, 1H, −NH-); ^{13}C NMR (400 MHz, DMSO): δ 21.22, 21.46, 21.75, 25.36, 27.82, 122.22, 129.92, 132.84, 136.95, 139.71, 139.77, 144.15, 151.24, 161.46, 169.13, 171.93 ppm; MS: *m/z* 310 (M^+). *Anal*. Calcd. for $C_{16}H_{14}N_4O_3$: C, 61.53; H, 5.16; N, 17.94; O, 15.37. Found: C, 61.43; H, 5.19; N, 17.84; O, 15.42.

3-(5-Phenyl-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. White solid; R_f 0.30 (6:4 hexane-EtOAc); IR (KBr): 3186, 3149, 3078, 2950, 1668, 1579, 1467, 1161, 1030 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 1.84 (m, 2H, CH_2), 2.71 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 7.26–7.28 (m, 2H, Ar-H), 7.39–7.41 (t, 1H, Ar-H), 7.92–7.94 (m, 2H, Ar-H), 10.61 ppm (s, 1H, −NH-); ^{13}C NMR (400 MHz, DMSO): δ 20.22, 21.72, 23.36, 24.82, 118.21, 121.11, 128.14, 127.95, 131.65, 133.77, 135.15, 142.44, 146.46, 160.86, 165.95 ppm; MS: *m/z* 280 (M^+). *Anal*. Calcd. for $C_{15}H_{12}N_4O_2$: C, 63.82; H, 5.00; N, 19.85; O, 11.34. Found: C, 63.85; H, 5.03; N, 19.80; O, 11.41.

3-(5-(o-Tolyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-2H-indazol-4(5H)-one. Creamish solid; R_f 0.29 (6:4 hexane-EtOAc); IR (KBr): 3207, 3123, 2959, 1658, 1546, 1472, 1265, 1041 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 1.80 (m, 2H, CH_2), 2.68 (t, 2H, CH_2), 2.73 (s, 3H, $-CH_3$), 2.88 (t, 2H, CH_2), 7.24–7.34 (dd, 1H, Ar-H, $^3J = 8.8$ Hz), 7.37–7.41 (m, 2H, Ar-H), 7.90–7.92 (dd, 1H, Ar-H, $^3J = 8.8$ Hz), 10.28 ppm (s, 1H, −NH-); MS: *m/z* 294 (M^+). *Anal*. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04; O, 10.87. Found: C, 65.42; H, 4.74; N, 19.09; O, 10.85.

3-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. White solid; R_f 0.34 (6:4 hexane-EtOAc); IR (KBr): 3207, 3123, 2959, 1668, 1526, 1265, 1049 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 1.79 (m, 2H, CH_2), 2.67 (t, 2H, CH_2), 2.84 (t, 2H, CH_2), 7.21–7.23 (dd, 2H, Ar-H, $^3J = 8.4$ Hz), 7.87–7.89 (dd, 2H, Ar-H, $^3J = 8.4$ Hz), 10.38 ppm (s, 1H, −NH-); ^{13}C NMR (400 MHz, DMSO): δ 20.10, 20.83, 22.47, 72.15, 115.24, 122.00, 127.92, 128.77, 137.62, 140.66, 149.32, 161.72, 164.29; MS: *m/z* 314 (M^+). *Anal*. Calcd. for $C_{15}H_{11}ClN_4O_2$: C, 56.88; H, 4.14; Cl, 11.19; N, 17.69; O, 10.10. Found: C, 56.93; H, 4.11; Cl, 11.21; N, 17.61; O, 10.13.

3-(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Yellow solid; R_f 0.32 (6:4 hexane-EtOAc); IR (KBr): 3207, 3123, 2990, 2862, 1653, 1509, 1461, 1061 cm^{-1}; MS: *m/z* 358 (M^+). *Anal*. Calcd. for $C_{15}H_{11}BrN_4O_2$: C, 49.88; H, 3.63; Br, 22.12; N, 15.51; O, 8.86. Found: C, 49.98; H, 3.59; Br, 22.14; N, 15.41; O, 8.88.

3-(5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Creamish solid; R_f 0.36 (6:4 hexane-EtOAc); IR (KBr): 3223, 3149, 2990, 2862, 1653, 1509, 1437, 1061 cm^{-1}; MS: *m/z* 298 (M^+). *Anal*. Calcd. for $C_{15}H_{11}FN_4O_2$: C, 60.00; H, 4.36; F, 6.33; N, 18.66; O, 10.66. Found: C, 60.18; H, 4.29; F, 6.31; N, 18.60; O, 10.61.

3-(5-(4-Hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Creamish solid; R_f 0.31 (6:4 hexane-EtOAc); IR (KBr): 3227, 3193, 2966, 1628, 1522, 1456, 1217, 1041 cm^{-1}; MS: *m/z* 296 (M^+). *Anal*. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.40; H, 4.73; N, 18.78; O, 16.09. Found: C, 60.51; H, 4.75; N, 18.69; O, 16.04.

3-(5-(3-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Creamish solid; R_f 0.33 (6:4 hexane-EtOAc); IR (KBr): 3227, 3173, 2989, 1648, 1586, 1468, 1251, 1061 cm^{-1}; MS: *m/z* 314 (M^+). *Anal*. Calcd. for $C_{15}H_{11}ClN_4O_2$: C, 56.88; H, 4.14; Cl, 11.19; N, 17.69;

O, 10.10. Found: C, 56.94; H, 4.10; Cl, 11.22; N, 17.58; O, 10.05.

3-(5-(3-Bromophenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Yellow solid; R_f 0.36 (6:4 hexane-EtOAc); IR (KBr): 3442, 3226, 3143, 2986, 1642, 1566, 1447, 1241, 1051 cm^{-1}; MS: *m/z* 358 (M^+). *Anal*. Calcd. for $C_{15}H_{11}BrN_4O_2$: C, 49.88; H, 3.63; Br, 22.12; N, 15.51; O, 8.86. Found: C, 49.81; H, 3.54; Br, 22.08; N, 15.47; O, 8.84.

3-(5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Creamish solid; R_f 0.29 (6:4 hexane-EtOAc); IR (KBr) ν: 3314, 3171, 3042, 2937, 2856, 1758, 1589, 1527, 1492, 1433, 1049, 873, 756, 727 cm^{-1}; MS: *m/z* 314 (M^+). *Anal*. Calcd. for $C_{15}H_{11}ClN_4O_2$: C, 56.88; H, 4.14; Cl, 11.19; N, 17.69; O, 10.10. Found: C, 56.98; H, 4.11; Cl, 11.22; N, 17.58; O, 10.05.

3-(5-(2-Nitrophenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Yellow solid; R_f 0.28 (6:4 hexane-EtOAc); IR (KBr): 3226, 3143, 2988, 1632, 1546, 1424, 1231, 1061 cm^{-1}; MS: *m/z* 325 (M^+). *Anal*. Calcd. for $C_{15}H_{11}N_5O_4$: C, 55.05; H, 4.00; N, 21.40; O, 19.55. Found: C, 55.19; H, 4.04; N, 21.37; O, 19.52.

3-(5-(2,5-Dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Creamish solid; R_f 0.30 (6:4 hexane-EtOAc); IR (KBr): 3217, 3153, 2950, 1613, 1539, 1431, 1061 cm^{-1}; MS: *m/z* 340 (M^+). *Anal*. Calcd. for $C_{17}H_{16}N_4O_4$: C, 59.64; H, 5.30; N, 16.37; O, 18.69. Found: C, 59.69; H, 5.28; N, 16.32; O, 18.71.

3-(5-(3,4-Dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Creamish solid; R_f 0.32 (6:4 hexane-EtOAc); IR (KBr): 3187, 3153, 2980, 1623, 1569, 1431, 1051 cm^{-1}; MS: *m/z* 340 (M^+). *Anal*. Calcd. for $C_{17}H_{16}N_4O_4$: C, 59.64; H, 5.30; N, 16.37; O, 18.69. Found: C, 59.69; H, 5.26; N, 16.41; O, 18.72.

3-(5-(4-Nitrophenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Yellow solid; R_f 0.34 (6:4 hexane-EtOAc); IR (KBr): 3227, 3120, 2980, 1623, 1509, 1461, 1051 cm^{-1}; MS: *m/z* 325 (M^+). *Anal*. Calcd. for $C_{15}H_{11}N_5O_4$: C, 55.05; H, 4.00; N, 21.40; O, 19.55. Found: C, 55.19; H, 4.04; N, 21.42; O, 19.50.

3-(5-(2-Bromophenyl)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-3aH-indazol-4(5H)-one. Yellow solid; R_f 0.53 (6:4 hexane-EtOAc); IR (KBr): 3414, 3171, 3143, 2937, 2856, 1589, 1492, 1276, 1049 cm^{-1}; MS: *m/z* 358 (M^+). *Anal*. Calcd. for $C_{15}H_{11}BrN_4O_2$: C, 49.88; H, 3.63; Br, 22.12; N, 15.51; O, 8.86. Found: C, 49.97; H, 3.57; Br, 22.17; N, 15.47; O, 8.87.

Antimicrobial screening. The diverse biological screenings of indazole bearing oxadiazole derivatives inspire us to screen the newly synthesized compounds.

Table 2

Antibiotic sensitivity assay (concentration 250/500/1000 μg/mL).

Sr. No.	ODZ	*Pseudomonas aeruginosa*			*Proteus vulgaris*			*Escherichia coli*			*Staphylococcus aureus*			*Candida albicans*		
		250	500	1000	250	500	1000	250	500	1000	250	500	1000	250	500	1000
1.	01	1.1	1.2	1.3	R	1	1.2	1.1	1.2	1.4	1.1	1.2	1.5	1.1	1.5	1.9
2.	02	1.3	1.4	1.9	1.3	1.7	2.1	1.2	1.5	2	1.1	1.5	1.9	1.1	1.4	1.6
3.	03	1.2	1.3	1.5	1.1	1.4	1.6	1.3	1.4	1.9	1.2	1.6	2	1.2	1.5	2
4.	04	R	R	R	1.1	1.3	1.7	1.1	1.3	1.6	R	R	R	1.1	1.4	1.8
5.	05	1.4	1.6	2	1	1.2	1.4	R	R	R	1.1	1.2	1.5	1.2	1.5	2
6.	06	1	1.1	1.3	R	1.1	1.3	R	R	R	R	1	1.4	R	1.1	1.5
7.	07	R	1	1.1	1.1	1.6	1.8	1.4	1.5	2	1.1	1.2	1.3	1.1	1.3	1.7
8.	08	R	R	R	1.1	1.3	1.5	1.2	1.3	1.7	R	1	1.3	1	1.2	1.8
9.	09	1.1	1.2	1.5	1.2	1.4	1.7	1.3	1.5	2	1.1	1.2	1.5	1.1	1.2	1.7
10.	10	1.3	1.4	1.8	R	1.1	1.3	R	1	1	1.2	1.4	1.7	1	1.3	1.8
11.	11	1.3	1.5	1.7	R	1	1.2	1.1	1.3	1.6	1.1	1.3	1.5	1	1.2	1.5
12.	12	1.2	1.4	1.6	1.1	1.4	1.8	1.2	1.5	1.9	R	1.2	1.7	1.1	1.5	2
13.	13	1.4	1.6	2	1.3	1.7	2	1.1	1.3	1.5	R	1	1.2	R	1.1	1.4
14.	14	1.1	1.1	1.3	1.1	1.3	1.8	1.4	1.6	2	1.1	1.2	1.4	1	1.2	1.7
15.	15	R	R	R	R	R	R	1.2	1.5	1.7	1.6	1.8	1.4	1.5	2	1.1
16.	16	1.1	1.2	1.4	1	1.3	1.7	1.4	1.5	2	1.3	1.5	1.2	1.3	1.7	R
17.	A		1.8			1.8			1.9			1.9			—	
18.	CPD		2.2			2.1			2.1			2.2			—	
19.	GF		1.8			1.9			2.0			2.0			—	
20.	GRF		-			—			—			—			2.6	
21.	FLC		-			—			—			—			2.8	

ODZ, oxadiazole; R, resistant; A, ampicillin; CPD, cefpodoxime; GF, gatifloxacin, GRF, griseofulvin; FLC, fluconazole.
Note: Zone of inhibition interpretation is as follows.

1. Zone size <1.0 cm – R.
2. Zone size 1.0 to 1.5 cm – intermediate.
3. Zone size >1.5 cm – sensitive.

Standard antibiotic sensitivity assay concentration 40 μg/mL.

Many antimicrobial agents have been applied for treatment; still, the medical field needs extensive efforts for the development of new antimicrobial agents to overcome the highly resistant species of microbes. The newly synthesized compounds (01 to 20) were tested for antibacterial screening using agar well diffusion method against *Staphylococcus aurues* MTCC-96 and *Bacillus subtillitis* MTCC-441 bacterial strain where antifungal screening using agar well diffusion method against *Aspergillus niger* MTCC-282 and *Candida albicans* MTCC-227 at different concentrations (50, 100, and 250 μg/mL), which were compared with ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, and griseofulvin as standard drugs. *S. aurues* MTCC-96 (Gram-positive bacteria) were grown in nutrient broth and *B. subtillitis* MTCC-441 (Gram negative bacteria) in peptone water (1% bacteriological peptone and 0.5% NaCl) for 24 h; this gave an optimum growth of the best bacteria. Each purified compound are dissolve in DMF sterilized using filtration (sintered glass filter) and store at 4°C. Out of all the solvents, DMF is used because of its good polarity and because it is easily removable. Each agent was then added to molten nutrient agar in the 0- (control), 50-, 100-, and 250-μg/mL concentration and poured into sterile petri dish. The pH of the media was maintained at 7.2–7.4. These were then spot inoculated on nutrient agar plates containing increasing amount of a compound, incubated at 37°C up to 24 h for determination of the minimum inhibitory concentration. Antifungal activity carried out using cup-plate method. The linear growth of the fungus was obtained by measuring the diameter of the fungal colony after 24 h. After 24-h incubation at 37°C, the zone of inhibition was measured in millimeter. The results are depicted in Table 2.

There are many methods well known for the synthesis of indazole bearing oxadiazole derivatives. Here, we report the acid catalyzed cyclocondensation method for the synthesis of oxadiazole and then indazole derivatives.

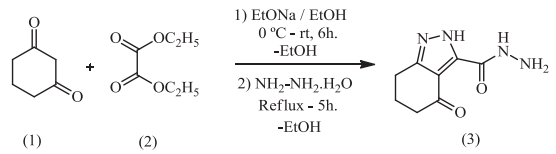


Figure 3. Synthesis of 4-oxo-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (**3**).

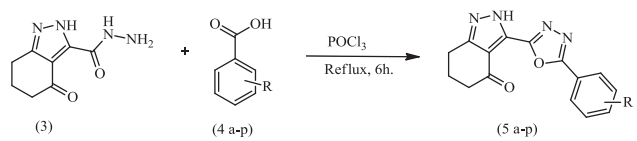


Figure 4. Synthesis of substituted indazole bearing oxadiazole derivatives (**5a–p**).

The one pot multi component synthetic strategies to achieve indazole bearing oxadiazole derivatives are shown in Figures 3 and 4. The structures of compounds were elucidated by various analytical tools like mass, IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

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