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Synthesis and biological evaluation of some new indazole-3-carboxamide derivatives

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ABSTRACT

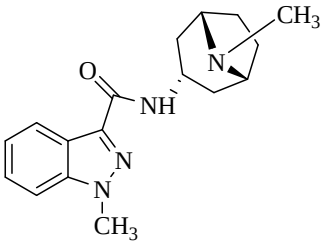
Fourteen new 1H-Indazole-3-carboxamides were synthesized by the coupling of substituted aryl or aliphatic amines of 1-H-Indazole-3-carboxylic acid which was obtained by introducing CO_2 group using n-butyl lithium from SEM protected Indazole.

Keywords: 1*H*-indazole; 1*H*-indazole-3-carboxamide; SEM-chloride; antimicrobial activity.

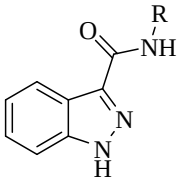
INTRODUCTION

Bicyclic aromatic heterocycles containing nitrogen and oxygen atoms, such as quinolones, indoles and benzofurans are ubiquitous in pharmaceuticals and natural products and many of them exhibit unique biological activities. The Indazole is a crucial heterocyclic skeleton often associated with biological activity. A number of derivatives of Indazole are known to possess potent pharmacological activity including anti-inflammatory, anti-tumor or HIV protease inhibition,[1,2] and inhibition of protein kinase C-B/AKt inhibitors.[3] In fact, compounds containing the Indazole skeleton are known to show a variety of biological activities such as high binding affinity for estrogen receptor,[4] antifungal, antibacterial activity.[5] Among the important heterocycles, many of the natural and synthetic Indazole–based heterocycles with diverse mechanism of action have been reported as lead anticancer,[6] 5-HT_2, 5-HT_3 and 5-HT_4 receptor antagonisms.[7-9]

The search for an efficient synthesis of the indazole ring system has been a long standing goal. However to date, methods reported for the synthesis of indazoles have met with only limited success. Most of the syntheses of the indazole derivatives reported in the literature proceed from benzene precursors in which the pyrazole moiety was generated by ring closure starting from isatins, phenylhydrazines or o-toluidines.[10-11] However, efficient methods for the introduction of electrophiles at the 3-position of indazoles are very difficult and can only be achieved by quite limited approaches.[12-14]



Granisetron



Title compounds

Chart-1 References and Title compounds

The aim of the present study was to identify tethering positions for potentially bulky biophysical tags on the high affinity 5-HT_3 antagonist granisetron [15] (Chart-1). The current synthesis of granisetron utilizes indazoles as starting material. The development of reliable and efficient method for the preparation of these indazoles was required to provide access to large quanties of bulk drugs for the studies.

MATERIALS AND METHODS

Chemicals and solvents used were either purchased from commercial suppliers or purified by standard techniques. All the experiments involving air-sensitive reagents were performed under an inert atmosphere in oven-dried glassware. The monitoring of reaction and checking of purity of the product were done using pre-coated **Merck silica gel 60 F_{254}** plates and compounds were visualized by irradiating with **UV** light or by exposing to **I_2** vapours, and or by staining with Ninhydrine stain followed by heating. Melting points were measured on a yanagimoto micro melting apparatus and are uncorrected. **IR** spectra were recorded on Perkin-Elmer 1420 spectrometer. **^{1}H NMR** spectra were recorded on Varian **400 MHz** spectrometer in **DMSO** as a solvent and **TMS** as an internal standard. The chemical shifts are reported in δ (ppm), and the residual signal of the solvent was used as the internal standard. High resolution mass spectra were obtained on a thermo finnigan **LCQ DECA XP MAX (ION TRAP) LCMSMS** mass spectrometer using direct infusion technique. Elemental analysis was performed on a Perkin-Elmer analyzer.

General procedure for the preparation of 1H-indazole-3-carboxilic acid (3): To a solution of 2 (11 g, 44.33 mmol) in dryTHF (60 mL) at -70 ^{0}C under nitrogen, was added n-BuLi (2.5 M in hexane, 19.49 mL, 48.76 mmol, 1.1 equiv) drop wise via addition funnel. The resulting bright yellow solution was stirred at the same temperature (- 70 ^{0}C) for 30 minutes. It was briefly warmed to 0 ^{0}C temperature for 10 minutes, re-cooled to - 40 ^{0}C, and CO_2 gas was passed into reaction mixture in small lots at - 40^{0}C, for 90 minutes. After 90 minutes the cooling bath was removed and the reaction was quenched by ammonium chloride solution (NH_4Cl, 50 mL). THF was stripped off and the residue was partitioned between diethyl ether (50 mL) and water. The separated aq. layer was neutralized with citric acid solution. The resulting solid material was filtered and dried in a oven at 35 ^{0}C (7.5 g, 58%). It was dissolved in mixable solvents of DMF (5 mL) and THF (50 mL) and treated with TBAF (1 M in THF, 98 mL, 0.35 mmol). The reaction mixture was refluxed at 80 ^{0}C for 4h and the reaction was monitored by TLC. After the evaporation of THF the residue was basified with 10% $NaHCO_3$ solution, washed with diethyl ether (50 mL × 2) and acidified with citric acid solution to generate solid material, which was filtered and dried in a oven at 35^{0}C to afford 4 g (yield - 98%) of **3.** Mp 259-262 ^{0}C; **IR (KBr**, cm^{-1}): 3280, 3186, 2945, 1687, 1588, 1518, 1486, 1382, 1282, 1174, 1149, 914, 779. **^{1}H NMR (DMSO):** δ 7.28 (t, 1**H**, ***J* = 5.6 Hz**), 7.44 (t, **1H**, ***J* = 5.8 Hz**), 7.64 (d, **1H, *J* = 6.4 Hz**), 8.04 (d, **1H, *J* = 6.0 Hz**), 13.01 (s, **1H**), 13.92 (s, **1H**). **MS (M$^+$ + 1):** 163.04, Anal. Calcd. For $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.22; H, 3.71; N, 17.25.

General procedure for the preparation of 1*H*-indazole-3-carboxamide derivatives (4a-n): To a solution of 3 (0.1 g, 0.61 mmol, 1 equiv) in DMF, HOBT (0.1 g, 0.74 mmol, 1.2 equiv), EDC.HCl (0.141 g, 0.74 mmol, 1.2 equiv) and TEA (0.187 g, 1.85 mmol, 3 equiv) were added and reaction mixture was stirred at RT for 15 minutes. The reaction mixture was treated with different amines (R) (0.61 mmol, 1 equiv) at RT and stirred for 4-6 h. The reaction was monitored by TLC, ice water (20 mL) was poured into reaction mixture and the liberated product was extracted with 10% of Methanol in Chloroform (30 mL × 2). The combined organic layer was washed with 10% $NaHCO_3$ (25 mL), brine solution and dried over Na_2SO_4. The solvent was evaporated under vacuo and the compound was purified by column chromatography (step gradient: 0-5% Methanol in $CHCl_3$) to afford **4a-n**. The yields are shown in Table 1.
N-benzyl-1H-indazole-3-carboxamide (4a): Mp 145-148 ^{0}C; **IR (KBr**, cm^{-1}): 3407, 3184, 1651, 1544, 1471, 1348, 1260, 1239, 1150, 1080, 956, 779, 680. **^{1}H NMR (DMSO):** δ 4.52 (d, **2H, *J* = 6.8 Hz**), 7.22-7.43 (m, **7H**), 7.64 (d, **1H, *J* = 8.0 Hz**), 8.21 (d, **1H, *J* = 8.2 Hz**), 9.08 (br, t, **1H**), 13.88 (s, **1H**). **MS (M$^+$ + 1):** 252.06.
N,N-diethyl-1H-indazole-3-carboxamide (4b): Mp 145-149 ^{0}C; **IR (KBr,** cm^{-1}): 3436, 3149, 2972, 1579, 1495, 1373, 1272, 1143, 1096, 941, 856, 750, 675. **^{1}H NMR (DMSO):** δ 1.23 (t, **6H**), 3.52-3.77 (m, **4H**), 7.28 (t, **1H, *J* = 5.4 Hz**), 7.42 (t, **1H, *J* = 5.8 Hz**), 7.64 (d, **1H, *J* = 6.4 Hz**), 8.04 (d, **1H, *J* = 6.2 Hz**), 13.76 (s, **1H**). **MS (M$^+$ + 1):** 218.14.

N-(2-morpholinoethyl)-1H-indazole-3-carboxamide (4c): Mp 148-151 ^{0}C; **IR (KBr,** cm^{-1}): 3416, 3175, 2970, 2856, 1644, 1538, 1471, 1372, 1296, 1157, 1048, 950, 864, 750. **^{1}H NMR (DMSO):** δ 2.42 (t, **4H**), 3.44 (q, **2H**), 3.59 (t, **6H**), 7.22 (t, **1H, *J* = 5.6 Hz**), 7.41 (t, **1H, *J* = 5.8 Hz**), 7.62 (d, **1H, *J* = 6.4 Hz**), 8.08 (d, **1H, *J* = 6.2 Hz**), 8.24 (brt, **1H**), 13.64 (s, **1H**). **MS (M$^+$ + 1):** 275.24.

(4-(2-fluorophenyl)pikperazin-1-yl)(1*H*-indazol-3-yl)methanone (4d): Mp 169-172 ^{0}C; **IR (KBr,** cm^{-1}): 3444, 3146, 3044, 2900, 2869, 1612, 1588, 1488, 1381, 1258, 1174, 1007, 909, 865, 740. **^{1}H NMR (DMSO):** δ 3.12 (brt, **4H**), 3.94 (brt, **2H**), 4.22 (brt, **2H**), 7.01 -7.24 (m, **5H**), 7.42 (t, **1H**, ***J* = 5.6 Hz**), 7.62 (d, **1H, *J* = 6.8 Hz**), 8.08 (d, **1H, *J* = 6.4 Hz**), 13.62 (s, **1H**). **MS (M$^+$ + 1):** 325.21.

(1*H*-indazol-3-yl)(4-(1-methylpiperidin-4-yl)piperazin-1-yl)methanone (4e): Mp 115-118 ^{0}C; **IR (KBr,** cm^{-1}): 3413, 2970, 1624, 1588, 1401, 1368, 1216, 1154, 1046, 928, 846, 755, 676. **^{1}H NMR (DMSO):** δ 1.82 (q, **4H**), 2.56 (s, **3H**), 2.84 (t, **4H**), 3.38 (t, **4H**), 3.67 (m, **2H**), 4.04 (brt, **2H**), 7.28 (t, **1H, *J* = 5.4 Hz**), 7.44 (t, **1H, *J* = 5.6 Hz**), 7.64 (d, **1H, *J* = 6.4 Hz**), 7.92 (d, **1H, *J* = 6.2 Hz**), 13.84 (s, **1H**). **MS (M$^+$ + 1):** 328.28, **MS (M$^+$ + 2):** 329.28.

N-(1-benzylpiperidin-4-yl)-1H-indazole-3-carboxamide (4f): Mp 178-181 ^{0}C; **IR (KBr,** cm^{-1}): 3415, 3059, 2919, 2860, 1671, 1584, 1482, 1380, 1280, 1153, 1084, 975, 831, 755. **^{1}H NMR (DMSO):** δ 2.24 (q, **4H**), 2.74 (t, **4H**), 3.46 (s, **2H**), 3.95 (m, **1H**), 7.32-7.44 (m, **6H**), 7.45 (t, **1H, *J* = 5.6 Hz**), 7.64 (d, **1H, *J* = 6.4 Hz**), 8.18 (d, **1H, *J* = 6.2 Hz**), 8.28 (brd, **1H**), 13.64 (s, **1H**). **MS (M$^+$ + 1):** 335.14, **MS (M$^+$ + 2):** 336.14

(1*H*-indazol-3-yl)(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)methanone (4g): Mp 195-198 ^{0}C; **IR (KBr**, cm^{-1}): 3142, 2892, 2844, 1616, 1599, 1508, 1446, 1384, 1282, 1230, 1127, 1050, 909, 868, 749. **^{1}H NMR (DMSO):** δ 3.42 (brt, **4H**), 4.01-4.26 (m, **4H**), 7.1-7.28 (m, **3H**), 7.44 (t, **1H, *J* = 5.6 Hz**), 7.58 (d, **2H, *J* = 7.4 Hz**), 7.66 (d, **1H, *J* = 6.4 Hz**), 8.03 (d, **1H, *J* = 6.2 Hz**), 13.82 (s, **1H**). **MS (M$^+$ + 1):** 375.08.

2-(4-(1*H*-indazole-3-carbonyl)piperazin-1-yl)benzonitrile (4h): Mp 170-173 ^{0}C; **IR (KBr**, cm^{-1}): 3413, 3154, 2902, 2817, 2224, 1663, 1607, 1539, 1488, 1377, 1257, 1145, 1075, 909, 840, 762. **^{1}H NMR (DMSO):** δ 2.94 (brt, **2H**), 3.44 (brt, **2H**), 3.92 (brt, **2H**), 4.25 (brt, **2H**), 7.11-7.34 (m, **3H**), 7.44 (t, **1H, *J* = 5.6 Hz**), 7.64-7.88 (m, **3H**), 8.04 (d, **1H, *J* = 6.0 Hz**), 13.82 (s, **1H**). **MS (M$^+$ + 1):** 331.94.

(1*H*-indazol-3-yl)(4-(pyridin-4-yl)piperazin-1-yl)methanone (4i): Mp 205-208 ^{0}C; **IR (KBr,** cm^{-1}): 3436, 2859, 1930, 1602, 1580, 1455, 1325, 1285, 1230, 1144, 1098, 992,905, 856, 760. **^{1}H NMR (DMSO):** δ 3.46 (brd, **4H**), 3.87 (brd, **2H**), 4.24 (brd, **2H**), 6.85 (d, **2H, *J* = 4.2 Hz**), 7.26 (t, **1H, *J* = 5.4 Hz**), 7.44 (t, **1H, *J* = 5.6 Hz**), 7.66 (d, **1H, *J* = 6.4 Hz**), 8.05 (d, **1H, *J* = 6.2 Hz**), 8.24 (d, **2H, *J* = 4.4 Hz**) 13.84 (brs, **1H**). **MS (M$^+$ + 1):** 308.23.

(1H-indazol-3-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone (4j): Mp 220-224 ^{0}C; **IR (KBr**, cm^{-1}): 3435, 3146, 3053, 2926, 2364, 1583, 1543, 1488, 1354, 1268, 1157, 1130, 1081, 982, 865, 785,689. **^{1}H NMR (DMSO):** δ 3.82-3.92 (m, **6H**), 4.24 (brt, **2H**), 7.26 (t, **1H, *J* = 5.4 Hz**), 6.77 (t, **1H, *J* = 5.6 Hz**), 7.66 (d, **1H, *J* = 6.2 Hz**), 8.06 (d, **1H, *J* = 6.0 Hz**), 8.42 (d, **2H, *J* = 2.4 Hz**), 13.82 (s, **1H**). **MS (M$^+$ + 1):** 309.12, **MS (M$^+$ + 2):** 310.12.

N-(2-(pyrrolidin-1-yl)ethyl)-1H-indazole-3-carboxamide (4k): Mp 120-123 ^{0}C; **IR (KBr**, cm^{-1}): 3402, 3151, 2944, 2884, 1644, 1580, 1538, 1466, 1370, 1270, 1248, 1149, 1053, 1002, 913, 848,771,639. **^{1}H NMR (DMSO):** δ 1.48 (m, **4H**), 1.78 (m, **4H**), 2.56 (t, **2H**), 3.48 (q, **2H**), 7.24 (t, **1H, *J* = 5.4Hz**), 7.41 (t, **1H, *J* = 5.6 Hz**), 7.63 (d, **1H, *J* = 6.4 Hz**), 8.18 (d, **1H, *J* = 6.2 Hz**), 8.24 (t, **1H, *J* = 2.4 Hz**), 13.84 (s, **1H**). **MS (M$^+$ + 1):** 259.18.

(1*H*-indazol-3-yl)(4-methylpiperazin-1-yl)methanone (4l): Mp 155-159 ^{0}C; **IR (KBr**, cm^{-1}): 3413, 2970, 1624, 1588, 1401, 1368, 1216, 1154, 1046, 928, 846, 755. **^{1}H NMR (DMSO):** δ 2.56 (s, **3H**), 3.32 (t, **4H**), 3.64 (t, **2H**), 4.08 (brt, **2H**), 7.24 (t, **1H, *J* = 5.4 Hz**), 7.44 (t, **1H, *J* = 5.6 Hz**), 7.64 (d, **1H, *J* = 6.4 Hz**), 7.92 (d, **1H, *J* = 6.2 Hz**), 13.82 (s, **1H**). **MS (M$^+$ + 1):** 245.15.

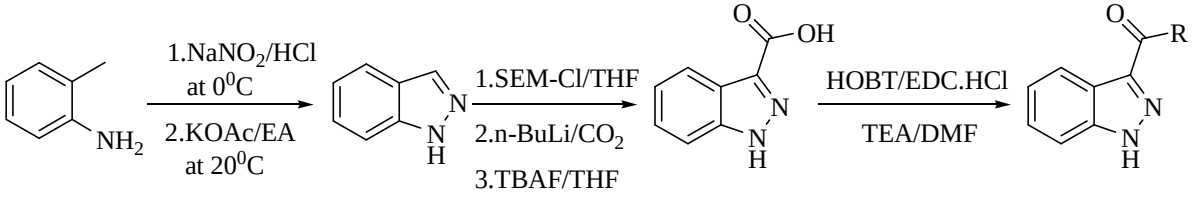
N-(4-methylbenzo[d]thiazol-2-yl)-1*H*-indazole-3-carboxamide (4m): Mp 225-228 ^{0}C; **IR (KBr**, cm^{-1}): 3339, 3154, 1675, 1574, 1471, 1328, 1250, 1239, 1150, 1070, 966, 775. **^{1}H NMR (DMSO):** δ 4.22 (s, **3H**), 7.28-7.38 (m, **4H**), 7.64 (d, **1H, *J* = 8.0 Hz**), 7.82-7.92 (m, **2H**), 9.03 (br, **t, 1H**), 13.88 (s, **1H**). **MS (M$^+$ + 1):** 309.16.

N-(1,3,4-thiadiazol-2-yl)-1H-indazole-3-carboxamide (4n): Mp 194-198 ^{0}C; **IR (KBr**, cm^{-1}): 3407, 3184, 1651, 1544, 1471, 1348, 1260, 1239, 1150, 1080, 956, 779. **^{1}H NMR (DMSO):** δ 7.28 (t, **1H, *J*=5.6 Hz**), 7.44 (t, **1H, *J* = 5.8 Hz**), 7.64 (d, **1H, *J* = 6.4 Hz**), 8.04 (d, **1H, *J* = 6.0 Hz**), 8.92 (s, **1H**), 13.01 (br, **1H**), 13.92 (s, **1H**). **MS (M$^+$ + 1):** 245.84, **(M$^+$ + 2):** 246.94.

RESULT AND DISCUSSION

The synthesis of 4a-n is shown in scheme-1 and it was accomplished starting from Indazole (2), which was prepared via diazotation of O-toluidine (1) [16-17]. A (2-Chloromethoxy-ethyl)-trimethyl-silane (SEM-Cl) protecting group was selectively attached to N - 2 of the Indazole (2), which was followed by a SEM-directed C-3 lithiation and subsequent reaction with CO_2 group, [18] and protecting group cleavage furnished indazole-3-carboxilic acid (3). Finally this was coupled with some substituted aryl or aliphatic amines (**R**) (Table-1) under amide coupling agent N-Hydroxybenzotrizole (HOBT), (3-Dimethylamino-propyl)-ethyl-carbodiimide (EDC.HCl) and triethyl amine (TEA), in N, N-Dimethyl-formamide (DMF) to yield amides (**4a-n**).

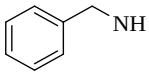
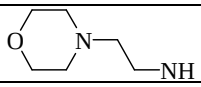
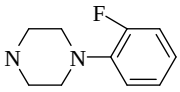
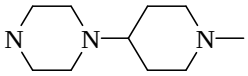
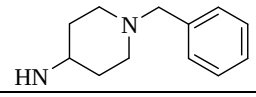
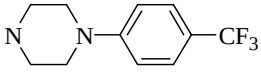
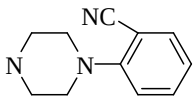
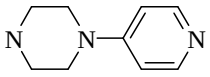
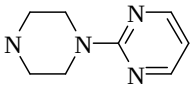
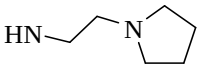
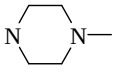
Scheme-1: Synthesis of 1*H*-indazole -3-carboxmides

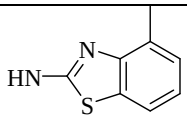
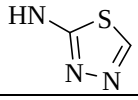


1 **2** **3** **4a-n**

The results in Table 1 demonstrate the significance of the present indazole-3-carboxamides synthesis (**4a-n**) from indazole-3-carboxilic acid (**3**) and amines (**R**). This confirms that using very simple experimental conditions, good yields can be achieved for awide range of differently substituted substrates. The structures of all the new synthesized compounds were confirmed by spectral data and elemental analysis. For example, the **^{1}HNMR** spectrum of **4a** shows signals at **9.0** (brt, **1H**, **CONH**) and **4.5** (d, **2H**, Ph **CH_2**), and the **IR** spectrum of **4a** exhibited the amide group **N-H** stretching frequency at about **3184** cm^{-1} and one typical amide carbonyl absorption for the amide moiety (**C=O**) at **1651** cm^{-1}. Finally, the structure assigned for this reaction product was fully supported by its elemental analysis.

Table 1. Characterization data of various compounds prepared (4a - n).

Compound	R	Yield (%) [a]	Calcd (%) (Found) C	H	N
4a		84	71.70 (71.48	5.21 5.16	16.72 16.67)
4b		87	66.34 (66.24	6.96 6.80	19.34 19.23)
4c		94	61.30 (61.22	6.61 6.45	20.42 20.36)
4d		93	66.65 (66.60	5.28 5.12	17.27 17.19)
4e		93	66.03 (65.94	7.70 7.61	21.39 21.28)
4f		96	71.83 (71.76	6.63 6.52	16.75 16.63)
4g		94	60.96 (60.87	4.58 4.43	14.93 14.89)
4h		84	68.87 (68.80	5.17 5.07	21.13 21.03)
4i		95	66.43 (66.33	5.58 5.47	22.79 22.69)
4j		89	62.32 (62.22	5.23 5.12	27.26 27.16)
4k		88	65.09 (64.98	7.02 6.93	21.69 21.55)
4l		65	63.91 (63.82	6.60 6.52	22.93 22.84)

4m		44	62.32 (62.24	3.92 3.86	18.17 18.11)
4n		38	48.97 (48.89	2.88 2.79	28.55 28.46)

[a] *Isolated yields*

Biological activity:

Antibacterial activity: The compounds **4a-n** were screened for their antibacterial activity against human pathogenic bacteria such as Escherichia coli (MTCC46), Pseudomonas aeruginosa (MTCC442), Staphylococcus aureus (MTCC87) and Streptococcus pyogene. The minimum inhibition concentration (MIC) was determined using the tube dilution method. [19] DMF was used as a blank and Ciprofloxacin as standard and the results are reported in Table 2.

Table 2. In Vitro antibacterial activity for compounds 4a-n

Compoun	Zone of Inhibition (mm)			
	Escheric coli	Pseudomo aerugino	Staphylococ aureus	Streptococ pyogene
4a	12	12	12	14
4b	12	11	12	14
4c	10	09	14	13
4d	09	-	-	-
4e	10	14	11	09
4f	13	13	12	14
4g	12	13	11	10
4h	12	14	12	13
4i	13	12	12	13
4j	13	11	15	13
4k	09	-	13	11
4l	11	10	12	13
4m	10	12	13	12
4n	12	13	11	14
Ciprofloxa	17	21	21	23

Most of the compounds **4a-c, 4e-j, 4l-m** and **4n** showed moderate activity against Escherichia coli, Pseudomonas aeruginosa, staphylococcus aureus and streptococcus pyogene. Compound **4d** had exhibited some activity against Escherichia coli, but didn't exhibit activity against Pseudomonas aeruginosa, staphylococcus aureus and streptococcus pyogene. Compound **4k** exhibited moderate activity against Escherichia coli, staphylococcus aureus and streptococcus pyogene, but didn't exhibit activity against Pseudomonas aeruginosa.

Antifungal Activity: The compounds **4a-n** were screened also for antifungal activities (Table 3) against Aspergillusniger and Helminthosporiumoryzae using fungicide Griseofulvin in DMF as the standard. The activity of compounds **4a-n** reffered in Table 3 was compared with that of the antifungal drug Griseofulvin.

Table 3. In Vitro antifungal activity for compounds 4a-n

Compound	Zone of Inhibition (mm)	
	Aspergillus niger	Helminthosporium oryzae
4a	12	13
4b	10	11
4c	10	12
4d	09	11
4e	10	09
4f	08	07
4g	12	11
4h	12	09
4i	13	-
4j	12	11
4k	11	12
4l	11	10
4m	10	12
4n	12	13
Griseofulvin	15	14

Most of the compounds **4a-h** and **4j-n** showed moderate activity against fungi Aspergillusniger and Helminthosporiumoryzae. Compound **4i** showed moderate activity against fungi Aspergillusniger, but didn't exhibit activity against fungi Helminthosporiumoryzae.

CONCLUSION

A new series of derivatives of new indazole-3-carboxamide, The structure of these compounds was confirmed by their IR, 1H NMR, and MS spectral data.

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