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SYNTHESIS OF SOME NEWER INDAZOLYL-OXADIAZOLES, THIADIAZOLES AND 1,2,4-TRIAZOLES

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تخليق بعض الإندازوليل - أكسا ثنائي الآزول ، ثيا ثنائي الأزول ، ١ , ٢ , ٤ - ثلاثي الآزول - الجديدة

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أمكن الحصول على إنتاج ممتاز من ٢ - آرايل - ٣ كلورو - ٢ H - إنـدازول وذلك بتـأثير كلوريد الثيونيل على تفاعل التكثيف بين آرثو - أزيدوبنزانيليد وإيثيل بارا - أمينو بنزوات منتجا مشتقات الإستر - اندازولو المقابلة . وقد تم تحويل مشتقات الأستر الناتجة إلى سلسلة جديدة من نظام ٢ - آرايل - اندازول المحتويه على اكسـاثنائي الآزول ، ثيا ثنائي الآزول ، ١ , ٢ , ٤ - ثلاثي الآزول . وتمت دراسـة النشـاط البيـولوجي لبـعض هذه المركبات .

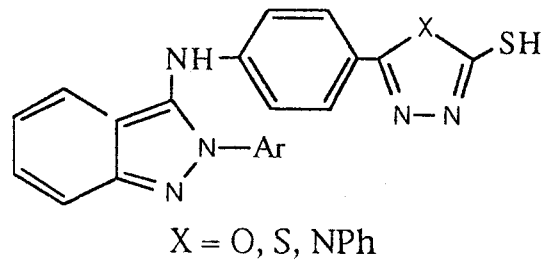
Key Words: Chloroindazoles, Ureidoindazoles, Thiureidoindazoles, Oxadiazolylindazoles, Thiadiazolylindazoles, Triazolylindazoles, Thiosemicarbazido-indazoles, Biological activity.

ABSTRACT

2-Aryl-3-chloro-2H-indazole (4), obtained in excellent yield (>90%) by the action of thionyl chloride on o-azidobenzanilide(3), was allowed to condense with ethyl p-aminobenzoate to afford the corresponding indazolo-ester (6). This latter compound was converted into a new series of 2-aryl-indazole systems containing the potentially antimicorbial oxadiazole, thiadiazole and 1,2,4-triazole moieties (9,10, 13 & 14). Some of the newly synthesized compounds were tested for biological activity.

INTRODUCTION

In continuation of our research program directed towards the synthesis of novel heterocycles with potential biological applications[1-3], a new series of indazole systems linked to 1,2,4-triazole, 1,3,4-oxadiazole, mercapto-triazole and thiadiazole moieties[9-14] has been prepared. Literature survey revealed that 1,3,4-oxadiazoles have been reported to be biologically versatile compounds having bactericidal, fungicidal, herbicidal, analgetic[4,5], antiproteolytic, hypoglycemic, antiinflammatory, tranquilizing and central nervous system (CNS) depressant activities[4-8]. Also a number of urea, thiourea, amide derivatives and hydrazides[9-11] are reported to possess excellent anthelmintic activity. The above observations prompted us to synthesize the previously unreported series of indazole systems having the potentially biological active moieties.



X = O, S, NPh

EXPERIMENTAL

All melting points were measured on Electro thermal point apparatus and are uncorrected. Infrared spectra were recorded on Perkin Elmer 1310 infrared spectrophotometer using KBr pellets(cm^{-1}). ^1H NMR spectra were recorded on Varian EM 360 NMR spectrophotometer 60 MHz using TMS as an internal standard and in DMSO-d_6 solutions; chemical shifts in d ppm throughout. *o*-Azidobenzoic acid (1) and *o*-azidobenzoyl chloride (2) were prepared according to literature methods[12].

N-(*o*-Azidobenzoyl) phenylamine (3)[13]

o-Azidobenzoyl chloride (0.035 mol) was added dropwise to a cold stirred solution of aniline (0.03 mol) in pyridine (25 ml). The mixture was stirred for 30 min. then poured into cold water (200 ml) to precipitate the crude N-(*o*-azidobenzoylarylamines) (3) which were purified by crystallization from ethanol. Other aromatic amines were allowed to react with *o*-azidobenzoyl chloride in the same manner. Details in Table 1.

2-Aryl-3-chloro-2H-indazoles(4)[14]

A mixture of N-(*o*-azidobenzoyl)-phenylamine (5g) and thionyl chloride (20 ml) is heated under reflux until the IR spectrum of the solution showed the disappearence of any absorption at 2120 cm^{-1} (2-20 h). Excess of thionyl chloride was removed from the reaction mixture by co-distillation with toluene (2 x 25 ml); the residual oily or semi-solid crude 3-chloro-2-phenyl-2H indazole is absorbed on alumina and purified by column chromatography with toluene/hexane (3:1 v/v) as eluents.
Other products (4) were obtained in the same way. Details in Table 2.

2-Aryl-3-hydrazino-2H-indazoles (11b)
Method A

A mixture of 2-aryl-3-chloro-2H-indazole (4) (0.01 mol) and hydrazine hydrate (4 ml) in ethanol (30 ml) was refluxed for 3 hours. The white solid obtained after cooling was filtered off, washed with petroleum ether and dried. Crystallization from ethylacetate-petroleum ether (b.p. 60-80 °C) gave needles, Details in Table 3B

Method B

To a suspension of 2-aryl-3-methylthio-2H-indazole (11 g, 0.01 mol) in ethanol (25 ml), hydrazine hydrate (4 ml) was added, and the reaction mixture was heated under reflux for 4 hours. Evaporation of the excess of the solvent under reduced pressure gave a semi-solid which on titration with petrol-ether (b.p. 40-60 °C) gave a white solid which was filtered off and dried. Crystallization from ethylacetate - petroleum ether (b. p. 60-80 °C) gave products identical to those obtained from method (A).

2-Aryl-3-azido-2H-indazoles (11a)

A mixture of the chloro-compound (0.01 mol) sodium azide (5 equiv.) and DMF (75 ml) was heated in an oil bath at 90 °C for seven hours. Excess of DMF was removed under reduced pressure and the sticky liquid was titrated with water to give a white solid which was crystallized from aqueous ethanol.

Details in table (3C). IR (KBr) 2100 (N_3), 1610 (C=N).

3-Amino-2-aryl-2H-indazoles (11c)

The azide (11 a 0.05 mol) in aqueous ethanol (150 ml, 10: 90 v/v) and 10% Pd/C was stirred at 1 atm. of hydrogen and 80 °C for overnight. The reaction mixture was then filtered off free of the catalyst, and the solvent removed in vacuo whereby a white solid was obtained which was crystallized from ethanol, 86%, IR (KBr) 3410-3320 (NH_2), 1620 (C=N).

Preparation of the Amides (11 d)
General Method

To 3-amino-2-arylindazole (11c) (2g) in pyridine (30 ml) and kept in an ice bath, the acid chloride (1.1 equiv.) was added dropwise with stirring. The reaction mixture was stirred for 2 hours and then poured into ice water. The solid product obtained was filtered off, washed with water free of pyridine and then dried. Crystallization form glacial acetic acid gave white flakes or needles. IR(KBr) 3360-3300 (NH), 1680 (C=O), 1200 (C=S).

Preparation of 2-Aryl-3-ureido/thiureido indazoles (11e)
General Method

A mixture of the amine (11e, 1g) and the respective arylisocyanate or arylisothiocyanate (1.1 equiv.) in absolute ethanol (20 ml) was heated under reflux for 4 hours. The solid obtained after cooling was filtered off, washed with cold ethanol and then dried. Crystallization from aqueous ethanol gave a white solid. IR (KBr) 3350-3250 (NH), 1660 (C=O), 1200 (C=S)

2-Aryl-3-mercapto-2H-indazoles (11f)

A solution of the chloro-indazole (4) (0.01 mol) and (0.012 mol) in dry methanol (50 ml) was heated under reflux for 6 hours. The solid then precipitated was collected, washed with ethanol, then heated with aqueous sodium hydroxide (10%, 15 ml) at 50°C for 30 min. The reaction mixture was then cooled and acidified with acetic acid. The solid products obtained were crystallized from ethanol-ethyl acetate mixture. Details in Table 3D.

2-Aryl-3-methylthio-2H-indazoles (11g)

To a solution of 2-aryl-3-mercaptoindazole (11f) (0.01 mol) in sodium hydroxide (5%, 50 ml) was added methyl iodide (3 ml) and the resulting mixture was allowed to stir at room temperature for 8 hours. The solid thus formed was collected and crystallized from aqueous ethanol. Table 3E. ^1H NMR (DMSO-d_6), 2.80 (S, 3H, SCH_3), 7.60-7.20 (m, 9H, Ar-H).

2-Aryl-3(3', 5'-dimethylpyrazol-1-yl)-2H-indazoles (11i)

A mixture of the hydrazino-compound (0.005 mol) and acetylacetone (5 ml) in ethanol (25 ml) was heated under reflux for five hours. The product which separated on cooling was filtered off, dried and crystallized from ethanol as pale yellow needles.

Details in Table 3 I. ^1H NMR (DMSO-d_6), 2.40 (S, 3H, CH_3), 2.65 (S, 3H, CH_3), 6.25 (S, 1H, CH), 7.60-7.20 (m, 9H, Ar-H).

3-N-Alkyl-2-aryl-2H-indazoles (11h)

A mixture of the chloro-indazol (4) (0.01 mol) and the appropriate amine (methylamine, ethylamine, benzylamine, aniline, p-chloroaniline, p-toluidine or p-anisidine) (1 equiv.) in ethanol (60 ml) was heated under reflux for 8-10 hours. The excess of solvent was removed in vacuo.

2-Aryl-3-(*p*-anilino-5'-aryl-1', 3', 4'-oxadiazol-2-yl)-2H-indazole. (10)
General Method

To the hydrazone (8, 1g) dissolved glacial acetic acid (7 ml) was added a solution of ferric chloride (5 g) in water and the resulting reaction mixture was stirred for 2 hours. The mixture was then diluted with water and kept for overnight in the fridge. The solid which separated was filtered off, washed with water, dried and crystallized. Details in Table 5B.

2-Aryl-3(*p*-anilino-5'-N'-aryl-1', 3', 4'-thiadiazol-2-yl)-2H-indazole. (10)

To chilled conc. H_2SO_4 (10 ml) the thiosemicarbazide (12,1 g) was added portionwise with stirring. After the addition was complete, the solution was left to stand at room temperature for 2 hours. It was then poured on crushed ice and the separated solid filtered off, washed with water and crystallized from DMF/ethanol.

IR (KBr): 3290 (NH), 1620-1610 (C=N), ^{1}H NMR (DMSO-d6) 9.00 (S, 2H, 2NH), 8.40-7.40 (m, 18H, Ar-H). Table 5B.

4-Aryl-3-mercapto-5[3-(*p*-anilino-2-phenylindazolyl)]-1,2,4-triazoles (14) General Method.

A solution of the thiosemicarbazide (12, 1g) in KOH solution (50 ml, 2 mol/L) was refluxed for 4 hours. After cooling and acidification with HCl (2N), the solid product (14) obtained was filtered off, washed with water, dried and crystallized from ethanol. Details in Table 5D.

2-Aryl-3(*p*-anilino)-5'-mercapto-1', 2', 3', oxadiazol-2-yl)-2H-indazole (9)

To a suspension of the hydrazide (7, 1g) in ethanol (10 ml), KOH (0.5 g) in water (5 ml) and CS_2 (5 ml) were added. The reaction mixture was heated under reflux till the evolution of H_2S ceased (4 h). It was then cooled, diluted with water and acidified with conc. HCl. The solid that separated was collected by filtration, washed with water and crystallized from aqueous ethanol (Table 5A).

Preparation of the Hydrazones (8)

The appropriate aldehyde (0.012 mol) was added to a suspension of the hydrazide (7, 0.01 mol) in ethanol (100 ml) and the reaction mixture was heated under reflux for 5 h. The product separated after evaporating 50 ml. of ethanol. It was filtered off and crystallized. Details in Table 4C.

Preparation of the Hydrazides (7)

A mixture of the ester (6, 0.01 mol) in ethanol (75 ml) and hydrazine hydrate (10 equiv.) was heated under reflux for 6 hours. When about 40 ml of ethanol has been removed, a solid separated out, which was filtered off, and crystallized from ethanol.

IR (KBr) 3350-3300 (NH), 1670 (C=O) and 1610 (C=N)

^{1}H NMR (DMSO-d_6) for (7, X = H) 8.50 (b, S, 3H, CONHNH2), 5.90 (S, 1H, NH) and 7.50-7.10 (m, 13H, Ar-H).

2-Aryl-3(*p*-ethoxycarbonylanilino)-2H-indazoles (6)

A mixture of the chloro-indazole (4) (0.01 mol) and ethyl p-aminobenzoate (0.01 mol) in ethanol (150 ml) was heated under reflux for 12 hours. The solvent was then removed in vacuo and the impure product was purified by column chromatography (alumina and ethylacetate/petrol ether) gave pale yellow solid which was crystallized from ethanol. IR (KBr) 3225 (NH), 1660 (C=O), 1610 (C=N).

RESULTS

The synthesis of the previously unreported series of indazolo compounds linked to oxadiazole, thiadiazole and triazole moieties are reported.

Table 1
N-(*o*-Azidobenzoyl)-arylamines (3)

Compound	X	m. p.(° C)	Yield (%)	Lit. m.p.	Ref.
3	H	131	90	130	13
	4-Me	129	80	130	14
	4-OMe	119	74	120	14
	4-Cl	118	77	117	14
	4-NO_2	160	76	164	14

Table 2
2-(4X-C_6H_4)-3-Chloro-2H-indazoles (4)

Compound	X	m. p.(° C)	Yield (%)	Lit. m.p.	Ref.
4	H	33	90	34	14
	4-Me	76	92	78	14
	4-OMe	95	95	94	14
	4-Cl	125	97	126	14
	4-NO_2	158	93	158	14

Table 3A

2-(4X-C_6H_4)-3-Aminoindazoles (11c).

Compound	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11c	H	121	86	$C_{13}H_{11}N_3$ (209.2)
	Me	146	82	$C_{14}H_{13}N_3$ (223.3)
	OMe	139	77	$C_{13}H_{13}N_3O$ (139.3)
	Cl	149	80	$C_{13}H_{10}ClN_3$ (243.7)
	NO_2	165	71	$C_{13}H_{10}N_4O_2$ (254.2)

Crystallisation solvent (C. R): Ethanol

Table 3B

2-(4X-C_6H_4)-3-Hydrazinoindazoles (11b).

Compound.	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11b	H	130	83	$C_{13}H_{12}N_4$ (224.3)
	Me	152	81	$C_{14}H_{14}N_4$ (238.3)
	OMe	150	80	$C_{14}H_{14}N_4O$ (254.3)
	Cl	159	82	$C_{13}H_{11}ClN_4$ (258.7)
	NO_2	187	73	$C_{13}H_{11}N_5O_2$ (269.3)

C. R: Ethyl acetate: Petroleum ether

Table 3C

3-Azidoindazoles (11a)

Compound	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11a	H	151	78	$C_{13}H_9N_5$ (235.2)
	Me	145	75	$C_{14}H_{11}N_5$ (249.3)
	OMe	147	74	$C_{14}H_{11}N_5O$ (265.3)
	Cl	152	76	$C_{13}H_8ClN_5$ (269.7)
	NO_2	179	70	$C_{13}H_8N_6O_2$ (280.2)

C. R: Aqueous ethanol

Table 3D

3-Mercaptoindazoles (11f).

Compound	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11f	H	65	85	$C_{13}H_{10}N_2S$ (226.3)
	Me	112	80	$C_{14}H_{12}N_2S$ (240.3)
	OMe	127	77	$C_{14}H_{12}N_2OS$ (256.3)
	Cl	145	74	$C_{13}H_9ClN_2S$ (260.7)
	NO_2	187	70	$C_{13}H_9N_3O_2S$ (271.3)

C. R: Ethanol: Ethyl acetate

Table 3E

3-Methylthioindazoles (11g)

Compound	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11g	H	119	82	$C_{14}H_{12}N_2S$ (240.3)
	Me	127	78	$C_{15}H_{14}N_2S$ (254.4)
	OMe	131	75	$C_{15}H_{14}N_2OS$ (270.4)
	Cl	153	73	$C_{14}H_{11}ClN_2S$ (274.8)
	NO_2	184	68	$C_{14}H_{11}N_3O_2S$ (285.3)

C. R: Aq. ethanol

Table 3F

N-Substituted Aminoindazoles (11h).

Compound	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11h	H	98	76	$C_{14}H_{13}N_3$ (223.3)
	Me	102	78	$C_{15}H_{15}N_3$ (237.3)
	OMe	112	75	$C_{15}H_{15}N_3O$ (253.3)
	Cl	120	70	$C_{14}H_{12}ClN_3$ (257.7)
	NO_2	131	65	$C_{14}H_{13}N_4O_2$ (269.3)

C. R: Ethanol

Table 3G
3-Amidoindazoles (11d)

Compound	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11d	H	179	90	$C_{20}H_{15}N_3O$ (313.3)
	Me	183	88	$C_{21}H_{17}N_3O$ (327.4)
	OMe	186	85	$C_{21}H_{17}N_3O_2$ (343.4)
	Cl	191	82	$C_{20}H_{14}ClN_3O$ (347.8)
	NO_2	212	69	$C_{20}H_{14}N_4O_3$ (358.3)

C. R: Acetic acid

Table 3H
3-Ureido-and 3-Thiureidoindazoles (11e)

Compound	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11e	H	186	77	$C_{20}H_{16}N_4O$ (328.4)
	Me	189	72	$C_{21}H_{18}N_4O$ (342.4)
	OMe	182	75	$C_{21}H_{18}N_4O_2$ (358.4)
	Cl	192	70	$C_{20}H_{15}ClN_4O$ (362.8)
	NO_2	215	61	$C_{20}H_{15}N_5O_3$ (373.4)
11e'	H	189	69	$C_{20}H_{16}N_4S$ (344.4)
	Me	202	72	$C_{21}H_{18}N_4S$ (358.5)
	OMe	209	70	$C_{21}H_{18}N_4OS$ (374.5)
	Cl	214	67	$C_{20}H_{15}ClN_4S$ (378.9)
	NO_2	225	64	$C_{20}H_{15}N_5O_2S$ (389.4)

C. R: Aq. ethanol

Table 3I
3-(3',5'-Dimethylpyrazol-1-yl)indazoles (11i)

Compound	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11i	H	201	75	$C_{18}H_{16}N_4$ (288.3)
	Me	209	70	$C_{19}H_{18}N_4$ (302.4)
	OMe	215	78	$C_{19}H_{18}N_4O$ (318.4)
	Cl	226	72	$C_{18}H_{15}ClN_4$ (322.4)
	NO_2	241	65	$C_{18}H_{15}N_5O_2$ (333.3)

C.R: Ethanol

Table 3J
Thiosemicarbazide-indazoles (11j)

Compound	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11j	H	191	82	$C_{20}H_{17}N_5S$ (359.4)
	Me	205	80	$C_{21}H_{19}N_5S$ (373.5)
	OMe	212	77	$C_{21}H_{19}N_5OS$ (389.5)
	Cl	223	75	$C_{20}H_{16}ClN_5S$ (393.9)
	NO_2	251	71	$C_{20}H_{16}N_6O_2S$ (404.4)

C. R: Aq. ethanol

Table 3K
Semicarbazide-Indazoles (11k).

Compound	Y	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
11k	H	182	70	$C_{20}H_{17}N_5O$ (343.4)
	Me	189	73	$C_{21}H_{19}N_5O$ (357.4)
	OMe	201	71	$C_{21}H_{19}N_5O_2$ (373.4)
	Cl	214	74	$C_{20}H_{16}ClN_5O$ (377.8)
	NO_2	259	70	$C_{20}H_{16}N_6O_3$ (388.4)

C. R: Aq. ethanol

Table 4A

3-(*p*-Ethoxycarbonylanilino)-indazoles (6):

Compound	X	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
6	H	142	65	$C_{22}H_{19}N_3O_2$ (357.4)
	Me	156	62	$C_{23}H_{21}N_3O_2$ (371.4)
	OMe	161	60	$C_{23}H_{21}N_3O_3$ (387.4)
	Cl	178	61	$C_{22}H_{18}ClN_3O_2$ (391.8)
	NO_2	189	58	$C_{22}H_{18}N_4O_4$ (402.4)

C. R: Ethanol

Table 4B

3-(*p*-Hydrazidoanilino)indazoles (7):

Compound	X	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
7	H	198	90	$C_{20}H_{17}N_5O$ (343.4)
	Me	212	85	$C_{21}H_{19}N_5O$ (357.4)
	OMe	206	84	$C_{21}H_{19}N_5O_2$ (373.4)
	Cl	219	80	$C_{20}H_{16}ClN_5O$ (377.8)
	NO_2	234	76	$C_{20}H_{16}N_6O_3$ (388.4)

C.R: Ethanol

Table 4C

3-(*p*-Arylideneanilino)indazoles (8):

Compound	X	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
8	H	211	65	$C_{27}H_{21}N_5O$ (431.5)
	Me	217	80	$C_{28}H_{23}N_5O$ (445.5)
	OMe	222	75	$C_{28}H_{23}N_5O_2$ (461.5)
	Cl	230	80	$C_{27}H_{20}ClN_5O$ (465.9)
	NO_2	249	70	$C_{27}H_{20}N_6O_3$ (476.5)

C.R: Ethanol

Table 4D

3-(p-Thiosemicarbazidoanilino)indazoles(12):

Compound	X	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
12	H	176	85	$C_{27}H_{22}N_6OS$ (478.6)
	Me	210	82	$C_{28}H_{24}N_6OS$ (492.6)
	OMe	219	80	$C_{28}H_{24}N_6O_2S$ (508.6)
	Cl	240	78	$C_{27}H_{21}ClN_6OS$ (513.0)
	NO_2	265	74	$C_{27}H_{21}N_7O_3S$ (523.6)

C.R: Methanol

Table 5A

5'-Mercapto-1,3,4-oxadiazoloindazoles (9):

Compound	X	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
9	H	195	84	$C_{21}H_{15}N_5OS$ (385.4)
	Me	204	79	$C_{22}H_{17}N_5OS$ (399.5)
	OMe	212	81	$C_{22}H_{17}N_5O_2S$ (415.5)
	Cl	223	77	$C_{21}H_{14}ClN_5OS$ (419.9)
	NO_2	237	72	$C_{21}H_{14}N_5O_3S$ (430.4)

C. R: Aq. Ethanol

Table 5B

5'-Phenyloxadiazoloindazoles (10)

Compound	X	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight
10	H	213	72	$C_{27}H_{19}N_5O$ (429.5)
	Me	219	70	$C_{28}H_{21}N_5O$ (443.5)
	OMe	222	68	$C_{28}H_{21}N_5O_2$ (459.5)
	Cl	229	65	$C_{27}H_{18}ClN_5O$ (436.9)
	NO_2	233	61	$C_{27}H_{18}N_6O_3$ (474.5)

C. R: Ethanol/DMF

Table 5C

2'-Phenylaminothiadiazoloindazoles (13):

Compound	X	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight	
13	H	215	69	$C_{27}H_{20}N_6S$	(460.5)
	Me	221	65	$C_{28}H_{22}N_6S$	(474.6)
	OMe	218	61	$C_{28}H_{22}N_6OS$	(490.6)
	Cl	227	60	$C_{27}H_{19}ClN_6S$	(494.9)
	NO_2	242	55	$C_{27}H_{19}N_7O_2S$	(505.5)

C. R: Ethanol/DMF

Table 5D

4'-Aryl-3'-mercapto-1,2,4-triazoloindazoles (14).

Compound	X	m. p.(° C)	Yield (%)	Mol. Formula & Mol. Weight	
14	H	182	81	$C_{27}H_{20}N_6S$	(460.5)
	Me	189	80	$C_{28}H_{22}N_6S$	(474.6)
	OMe	193	78	$C_{28}H_{22}N_6OS$	(490.6)
	Cl	205	76	$C_{27}H_{19}ClN_6S$	(494.9)
	NO_2	226	72	$C_{27}H_{19}N_7O_2S$	(505.5)

C. R: Ethanol

The microanalyses for the new compounds were in satisfactory agreement with the values calculated (C ± 0.19, H ± 0.12, N ± 0.15).

Table 6

Minimum Inhibitory Concentrations (M.I.C) of compounds 7-9 against different organisms.

	M. I. C ($mgml^{-1}$)		
Compound	Staphylococcus aureus	Bacillus subtilis	Escherichia coli
7, X = H	240	237	240
7, X = Me	241	219	241
7, X = OMe	241	230	237
7, X = Cl	240	229	229
7, X = NO_2	246	230	246
8, X = H	217	216	240
8, X = Me	237	230	239
8, X = OMe	239	217	244
8, X = Cl	230	219	237
8, X = NO_2	240	231	241
9, X = H	231	240	244
9, X = Me	241	227	231
9, X = OMe	237	229	237
9, X = Cl	240	238	231
9, X = NO_2	244	230	237

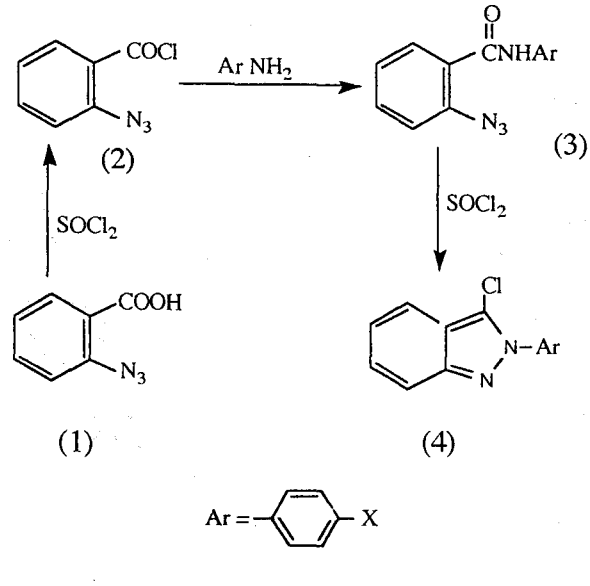
Penicillin (as reference)

BIOLOGICAL ACTIVITY

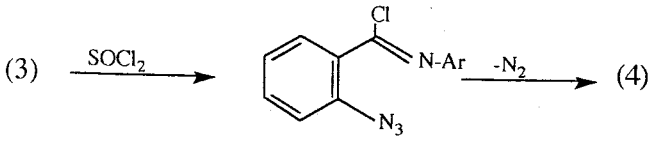
Biological screening of selected compounds (7), (8) and (9) was carried out to evaluate their antibacterial properties. Preliminary screenings of the tested compounds (7-9) against different strains of both Gram positive and Gram negative bacteria were determined using the filter paper disc method(16). Determination of the minimum inhibitory concentration of the tested compounds against Staphylococcus aureus, Bacillus subtilis and Escherichia coli using the agar-cup-diffusion method(17) and using penicilin (100 unit) as a reference was carried out. The results are listed in table (6). The activity of other compounds was not significant.

DISCUSSION

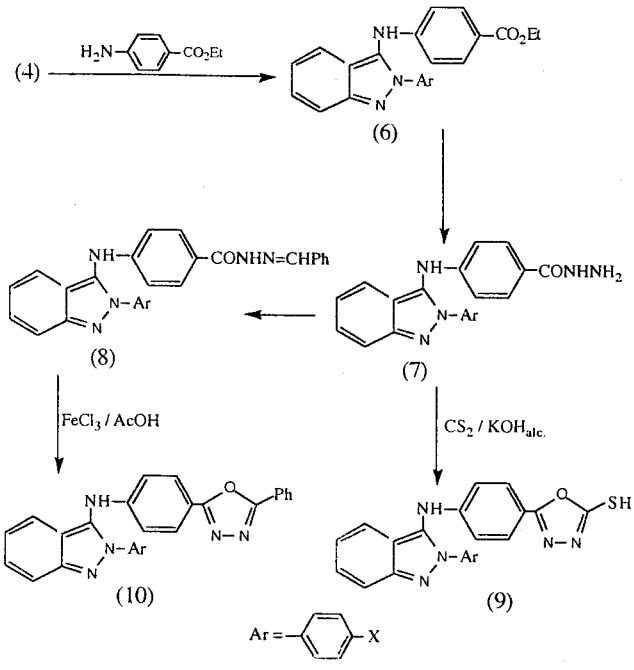
The intermediate 2-aryl-3-chloro-2H-indazole (4), was obtained in excellent yield by treatment of o-azidobenzoylanilide (3) with hot thionyl chloride(14). These azidoanilides were in turn[12, 13] prepared in high yield by reacting the acid chloride (2) with the appropriate aromatic amines in pyridine solution as outlined.



The mechanism of 2-aryl-3-chloroindazole (4) formation is not yet clear(14). However, it is most likely that o-azidobenzimidoyl chlorides (5) are formed initially, followed by a concerted pericyclic process with loss of nitrogen as proposed by Dyall(15) for the ring closure of similar systems. The possibility of the formation of a nitrene intermediate during the assisted cyclization of (3) at such mild reaction conditions (80°C) is not possible(15); instead cyclization via a concerted non-nitrenoid mechanism is more likely.

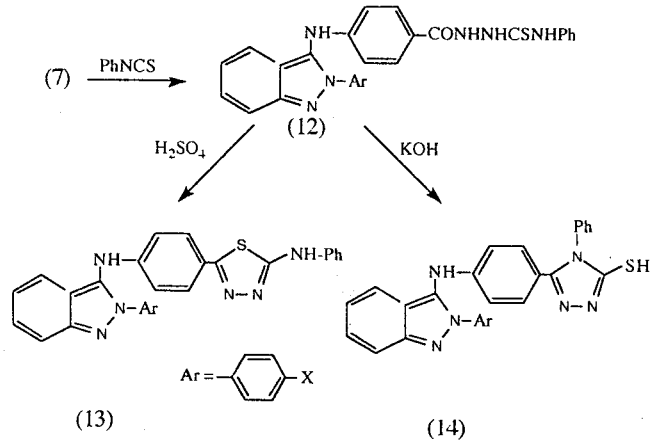


Condensation of the chloro-indazole (4) with ethyl *p*-aminobenzoate in ethanol proceeded smoothly to give the arylamine derivatives (6) in fair yields. Refluxing the latter compound with hydrazine hydrate produced the acid hydrazides (7) in good yield. Condensation of these hydrazides with benzaldehyde yielded the corresponding hydrazones (8). These Schiff bases exhibited the bands 3190-3160 (NH), 1675-1650 (CONH) and 1615-1580 (C=N); the ^{1}H NMR showed peaks at 9.6-9.2 (CONH), 8.5-8.3 (CH=N), 7.4-7.1 (m, 18H, Ar) and 5.5 (NH).

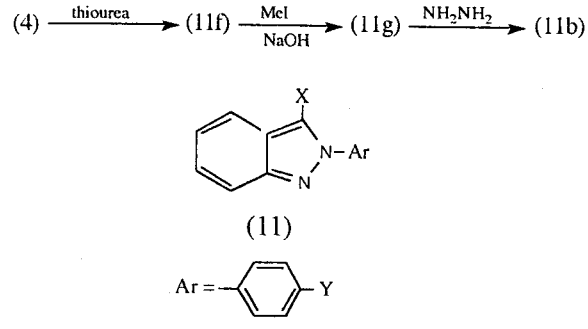


Refluxing the acid hydrazide (7) with equimolecular amount of ethanolic KOH and slight excess of carbon disulfide for 4 hours afforded an excellent yield of the corresponding 5-mercapto-1,3,4-oxadiazoles(9). 5'-Phenyloxadiazoles (10) were achieved by the oxidative cyclization of the Schiff bases (8) with $FeCl_3$ in acetic acid. The IR spectrum of the oxadiazoles (10) displayed peaks at 3400, 1640 and 1020 for NH, C=N and C-O-C functions, respectively. The 3-chloro-indazoles (4) were easily converted into the corresponding hydrazino (11b) and azido derivative (11a) by reacting (4) with hydrazine hydrate and sodium azide, respectively.

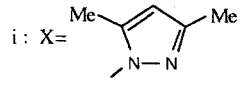
The hydrazino-derivatives (11b) were heated with acetylacetone, arylisocyanates and arylisothiocyanates in absolute ethanol to afford 2-aryl-3-(3', 5'-dimethyl pyrazol-1-yl) indazole (11i), the semicarbazides (11k) and the thiosemicarbazides (11j) respectively. 3-Aminoindazoles (11c) were obtained by the catalytic reduction of the azide (11a). The urea and thiourea (11e & 11e') derivatives were obtained by reacting 3-aminoindazoles (11c) with arylisocyanates and arylisothiocyanate, respectively, in absolute ethanol. The thiosemicarbazides (12) obtained by heating under reflux a mixture of the hydrazide (7) and an equivalent quantity of arylisothiocyanate in absolute ethanol, cyclized to give new products depending on the reagent used. Using KOH solution, 4-aryl-3'-mercapto-1,2,4-triazolo derivatives (14) were achieved in good yields; while using Conc. H_2SO_4 5'-arylamino-1,3,4-thiazoles (13) were obtained.



The N-substituted aminoindazoles (11h) and the amides (11e) were achieved in good yield by allowing (4) and (11c) to react independantly with the appropriate amines in ethanol solution and acid chlorides/pyridine, respectively. 3-Hydrazinindazole (11b) was also obtained by a different method. The chloro-compound (4) was reacted with thiourea to give the corresponding mercaptoindazole (11f). Methylation of (11f) with methyl iodide yielded the methyl thioindazole (11g). Condensation of (11g) with hydrazine hydrate furnished 3-hydrazino-indazole (11b). The identity of the product was matched with the product obtained from hydrazinolysis of (4).



a : X=N_3
b : X=$NHNH_2$
c : X=NH_2
d : X=NHCOPh
e : X=NHCONHPh
e':X=NHCSNHPh
f : X=SH
g : X=SCH_3
h : X=NHR (R=CH_3, CH_2CH_3)



j : X=NHNHCSNHPh
k: X=NHNHCONHPh

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