International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE
V-1, I-3, 2012

Synthesis and antimicrobial activity of some new indazolone derivatives from 1-(3,5-Dibromo-2-hydroxy-4 methyl phenyl) ethanone

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Manuscript No: IJPRS/V1/I3/00172, Received On: 14/09/2012, Accepted On: 20/09/2012

ABSTRACT

Indazolone nucleus is present in various therapeutically important drug candidates. Chalcones are possessing versatile pharmacological activities like anti-inflammatory, antifungal, antibacterial, antioxidant, cytotoxic, anticancer, antimalarial. While the bromoacetophenone nucleus bears very good antimicrobial activity. With consideration of all these facts we synthesized new derivatives of bromo acetophenone nucleus, which reacts with aromatic aldehydes to obtained chalcone. This was further derivatized to indazolone. All synthesized compounds were confirmed by spectral data and elemental analysis. The synthesized compounds were screened for antibacterial activity against *Staphylococcus epidermidis, Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and antifungal activity against *A. niger*. All synthesized compounds showed good to moderate antimicrobial activity.

KEYWORDS

1-(3,5-Dibromo-2-hydroxy-4 methyl phenyl)ethanone, Chalcone, Indazole, Antimicrobial Activity.

INTRODUCTION

Since many years bromo acetophenone nucleus has received remarkable attention due to associated with various therapeutic activities like antibacterial[1], anticancer[2], anti-HIV[3], anti-leishmanial[4] etc. Chalcones are subject of attention for research community. There is extensive analysis going on in this particular molecule due to its wide range of pharmacological activities like anti-inflammatory, antifungal, antibacterial, antioxidant, cytotoxic, antimalarial[5], antimitotic and many more. A number of heterocycles are synthesized from chalcone, which also shown a variety of pharmacological activities.

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Indazole, a five member, nitrogen containing ring system exhibits a variey of pharmacological activities like anticancer[6], antiasthametic[7], antipyretic[8], antiviral[9], antimicrobial[10], tyrosin kinase inhibitor. Indazole is also a core part of various bioactive molecules like Adjudin, a phase three molecule for male human contraceptive pill. Iodidamine, antichemotherapy drug that inhibit aerobic glycolysis cancer. Taking all these consideration into account with versatile properties of chalcone, cyclohexenone and indazole derivatives, we have synthesized molecules with hope to get better antimicrobial agents. By considering these facts we come on conclusion and report the synthesis of various chalcones from 1-(3,5-dibromo-2-hydroxy-4 methyl phenyl) ethanone and further derivatised into respective indazolone via intermediate cyclohexenone.

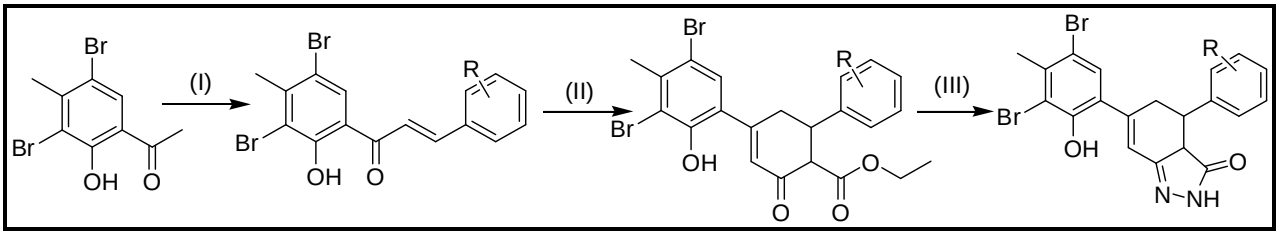
Chemistry

1-(3,5-Dibromo-2-hydroxy-4 methyl phenyl)ethanone (1) react with substituted acetophenones in 40% KOH to obtained chalcones(2a-2j). Chalcones are converted into corresponding cyclohexenone derivatives (3a-3j) by reaction with ethylacetoacetate and potassium carbonate in acetone, which further reacts with hydrazine hydrate with catalytic amount of glacial acetic acid in ethanol as a solvent, at reflux temperature to convert in to indazole derivatives (4a-4j). The constitution of the synthesized products have been characterized by using elemental analysis, infrared spectroscopy and ^{1}H-nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy.

1. General procedure for synthesis of ((2E)-1-(3,5-dibromo-2-hydroxy-4-methylphenyl)-3-phenylprop-2-en-1-ones (2a-2j)

To a solution of 1-(3,5-dibromo-2-hydroxy-4 methyl phenyl) ethanone (0.01mol) in ethanol (10ml) was added a solution of substituted aldehyde (0.01mol) in ethanol(10ml). To this mixture 40% KOH solution in ethanol was added drop-wise as to make it alkaline. The reaction mass was stirred for 18 hrs at room temperature.

Scheme



(1) (2a-2j) (3a-3j) (4a-4j)

Reaction condition: **(I)**Substituted aldehyde, 40%KOH, ethanol, 25^0C, 18hrs (R = different substitution) **(II)** ethylacetoacetate, K_2CO_3, acetone,reflux, 18hrs. **(III)** hydrazine hydrate(80%),catalytic glacial aceticacid, reflux, 6hrs

Experimental Procedure

All chemicals used in this study were purchased from Spectrochem limited. The melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR-8400 spectrophotometer using KBr disc and ^{1}H NMR spectra in $DMSOd_6$ or in $CDCl_3$ (Chemical shift in δ ppm) on Bruker spectrometer (400 MHz) using TMS as an internal standard. Elemental analysis of the all synthesized compounds was carried out on Euro EA 3000 elemental analyzer and the results are in agreement with the structure assigned. The purity of all compounds was checked by thin layer chromatography using TLC plates of silica gel (E.Merck G254) using Ethyl acetate : Hexane solvent system (7:3). Physical Constants, Spectral data and Elemental Analysis of synthesized compounds 4a-4j are recorded in Table – 1, 2, and 3 respectively.

2. General procedure for synthesis ethyl 4-(3,5-Dibromo-2-hydroxy-4-methylphenyl)-2-oxo-6-susbtituted phenylcyclohex-3-ene-1-carboxylates (3a-3j)

To a stirred solution of compound (2a-2j) (0.01mol) in dry acetone (20ml) was added ethylacetoacetate(0.01mol) and dry K_2CO_3 (0.02 mol). Stirred the reaction mass for 18hrs at reflux temperature. Cool down the solution and pour onto crushed ice. Neutralize with concentrated HCl and collect the precipitate of The product was isolated by filtration and crystallized using appropriate solvent.

the product. Filter in vacuo, dried and crystallized using an appropriate solvent.

3. General procedure for synthesis 6-(3,5-Dibromo-2-hydroxy-4-methyl phenyl)- 4-substituted phenyl-2,3a,4,5-tetrahydro-3Hindazol-3-ones (4a-4j)

To a stirred solution of cyclohexenone derivatives (3a-3j) (0.01mol) in ethanol (10ml) , hydrazine hydrate (0.01 mol) and catalytic amount of glacial acetic acid(1ml)was adddead and stirred the reaction mass at reflux condition for 6hrs.The solid product was separated upon cooling which was filtered, dried and crystallized using ethanol.

Antimicrobial activity

The antimicrobial activity was assayed by using the disc diffusion method. Newly synthesized compounds were screened *in vitro* for their antimicrobial activity against four bacterial strains such *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and fungi *Aspergillus niger* at 40 μg/mL concentration. Standard drugs like Amoxicillin and Greseofulvin were used for the comparison purpose. The obtained results for compounds 4a-4j are recorded Table 4.

Table 1: Physical constants of 6-(3,5-Dibromo-2-hydroxy-4-methylphenyl)-4-substituted phenyl- 2, 3a, 4, 5-tetrahydro-3Hindazol-3-ones (4a-4j)

Sr No.	Compound name	R	Molecular Formula	Mol. Weight	Yield	Melting Point	R_f
1	4a	C_6H_5-	$C_{20}H_{16}Br_2N_2O_2$	476	72%	220^0C	0.5
2	4b	3-Br- C_6H_4-	$C_{20}H_{15}Br_3N_2O_2$	555	60%	190^0C	0.57
3	4c	2-Cl-C_6H_4-	$C_{20}H_{15}Br_2Cl_2N_2O_2$	510	68%	160^0C	0.59
4	4d	4-Cl-C_6H_4-	$C_{20}H_{15}Br_2Cl_2N_2O_2$	510	70%	198^0C	0.52
5	4e	4-$N(CH_3)_2$-C_6H_4-	$C_{22}H_{21}Br_2N_3O_2$	519	65%	154^0C	0.67
6	4f	4-OCH_3-C_6H_4	$C_{21}H_{18}Br_2N_2O_3$	506	75%	140^0C	0.70
7	4g	3,4-OCH_3-C_6H_4	$C_{22}H_{20}Br_2N_2O_4$	536	60%	170^0C	0.45
8	4h	2-NO_2-C_6H_4-	$C_{20}H_{15}Br_2N_3O_4$	521	58%	182^0C	0.30
9	4i	3-NO_2-C_6H_4-	$C_{20}H_{15}Br_2N_3O_4$	521	60%	198^0C	0.38
10	4j	4-OH-C_6H_4-	$C_{20}H_{16}Br_2N_2O_3$	492	70%	167^0C	0.54

Table 2: Spectroscopic data of 6-(3,5-dibromo-2-hydroxy-4-methylphenyl)-4-substituted phenyl-2,3a,4,5-tetrahydro-3Hindazol-3-ones (4a-4j)

Sr. No.	Comp. No.	IR(KBr) ν(cm^{-1})	^{1}H NMR (δppm)
1	4a	3400-3600, 1670, 1605, 1517, 760	2.62(1H,m,CH_a), 2.82(3H,s,Ar-CH_3), 2.99(1H,m,CH_b), 3.38(1H,m,CH), 3.75(1H,dd, CH), 7.01(1H,m,CH), 7.32-7.45(5H, m, Ar-H), 7.52(1H,s,Ar-H) 9.39(1H,s, -CONH)
2	4b	3400-3600, 1670, 1605, 1517, 760	2.62(1H,m,CH_a), 2.82(3H,s,Ar-CH_3), 2.99(1H,m,CH_b), 3.13(1H,m,CH), 3.74(1H,m, CH), 7.33(1H,m,Ar-H),7.34(1H,d,Ar-H),7.48(1H,m,Ar-H), 7.52(1H,s,Ar-H), 7.58(1H, qd,Ar-H), 9.39(1H,s, -CONH)
3	4c	3400-3600, 1670, 1605, 1517, 760, 743	2.37(1H,m,CH_a), 2.82(3H,s,Ar-CH_3), 2.75(1H,m,CH_b), 3.66(1H,m,CH), 3.70(1H,m, CH), 7.01(1H,m,CH),7.14(1H,td,Ar-H),7.18(1H,dd,Ar-H),7.46(1H,td,Ar-H), 7.52(1H,s,Ar-H), 7.80(1H, dd,Ar-H), 9.39(1H,s, -CONH)
4	4d	3400-3600, 1670, 1605, 1517, 760, 743	2.62(1H,m,CH_a), 2.82(3H,s,Ar-CH_3), 2.99(1H,m,CH_b), 3.38(1H,m,CH), 3.74(1H,m, CH), 7.01(1H,m,CH),7.18(2H,dd,Ar-H),7.48(2H,dd,Ar-H), 7.52(1H,s,Ar-H), 9.39(1H,s, -CONH)
5	4e	3400-3600, 1670, 1605, 1517, 760	2.62(1H,m,-CH_a), 2.82(3H,s,Ar-CH_3), 2.90(6H,s,$N(CH_3)_2$, 2.99(1H,m,CH_b), 3.38(1H,m,-CH), 3.74(1H,m,CH),6.89(2H,dd,Ar-H), 7.01(1H,m,CH), 7.50(2H,dd,Ar-H),7.52(1H,s,Ar-H), 9.39(1H,s,CONH)
6	4f	3400-3600, 1670, 1605, 1517, 1100, 760	2.10(2H,dd,Ar-H), 2.62(1H,m,CH_a), 2.82(3H,s,Ar-CH_3), 2.99(1H,m,CH_b), 3.73(3H,s,CH), 3.38(1H,m, CH), 3.74(1H, m,CH), 7.01(1H,m,Ar-H), 7.17(2H,dd,Ar-H), 7.52(1H,s,Ar-H), 9.39(1H,s, CONH)
7	4g	3400-3600, 1670, 1605, 1517, 760	2.62(1H,m,CH_a), 2.82(3H,s,Ar-CH_3), 2.99(1H,m,CH_b), 3.32(1H,m,CH), 3.75(1H,m, CH), 3.74(3H,s,OCH_3), 3.77(3H,s,OCH_3), 6.79(1H,dd,Ar-H), 6.80(1H,d,Ar-H), 7.01(1H,s,CH), 7.08(1H,s,Ar-H), 7.52(1H,s,Ar-H), 9.39(1H,s, CONH)
8	4h	3400-3600, 1670, 1605, 1517, 1100, 760	2.82(3H,s,Ar-CH_3), 3.04(1H,m,CH_b), 3.41(1H,m,CH), 3.72(1H,m, CH), 3.85(1H,m,CH), 7.01(1H,m,CH), 7.30(1H,m,Ar-H), 7.52(1H,s,Ar-H),7.61(1H,td,Ar-H), 7.65(1H,dd,Ar-H),8.01(1H,dd,Ar-H), 9.39(1H,s, CONH)
9	4i	3400-3600, 1670, 1605, 1517, 1100, 760	2.62(1H,m,CH_a), 2.82(3H,s,Ar-CH_3), 2.99 (1H,m,CH_b), 3.74(1H,m,CH), 3.80(1H,m, CH), 7.01(1H,m,CH), 7.52(1H,s,Ar-H),7.62(1H,m,Ar-H), 7.66(1H,m,Ar-H), 7.91(1H,qd,Ar-H), 8.15(1H,t,Ar-H), 9.39(1H,s, CONH)
10	4j	3400-3600, 1670, 1605, 1517, 760	2.62(1H,m,CH_a), 2.82(3H,s,Ar-CH_3), 2.99 (1H,m,CH_b), 3.38(1H,s,CH), 3.74(1H,s, CH), 6.91(2H,dd,Ar-H), 7.01(1H,m,CH), 7.07(2H,dd,Ar-H), 7.52(1H,s,Ar-H), 9.39(1H,s, CONH)

Table 3: Elemental Analysis of Compounds 6-(3,5-dibromo-2-hydroxy-4-methylphenyl)-4-substituted phenyl-2,3a,4,5-tetrahydro-3Hindazol-3-ones (4a-4j)

Compound No.	**Elemental Analysis (Calculated)**				**Elemental Analysis (Found)**			
	%C	**%H**	**%O**	**%N**	**%C**	**%H**	**%O**	**%N**
4a	50.45	3.39	6.72	5.88	50.50	3.45	6.75	5.90
4b	53.28	2.72	5.76	5.05	53.30	2.75	5.80	5.07
4c	47.04	2.96	6.27	5.49	47.09	3.02	6.30	5.54
4d	47.04	2.96	6.27	5.49	47.10	3.05	6.35	5.55
4e	50.89	4.08	6.16	8.09	50.93	4.14	6.20	8.15
4f	49.83	3.58	9.48	5.53	49.88	3.65	9.50	5.58
4g	49.28	3.76	11.94	5.22	49.33	3.80	11.98	5.26
4h	46.09	2.90	12.28	8.06	46.12	2.94	12.30	8.10
4i	46.09	2.90	12.28	8.06	46.15	2.96	12.33	8.15
4j	48.81	3.28	9.75	5.69	48.85	3.32	9.78	5.74

Table 4: Antimicrobial screening results of compounds 4a-4j

	R- Substituion	**Antibacterial activity (%)**				**Antifungal activity (%)**
		S.aureu	*S.epidermidis*	*E.coli*	*P.aeruginosa*	*A. niger*
4a	C_6H_5-	80	33	50	67	50
4b	3-Br C_6H_4-	70	71	55	67	63
4c	2-Cl-C_6H_4-	60	54	86	48	67
4d	4-Cl-C_6H_4-	68	69	68	81	83
4e	3-N$(CH_3)_2$-C_6H_4-	65	75	77	43	50
4f	4-OCH_3-C_6H_4-	85	83	45	95	46
4g	3,4-di $OCH_3C_6H_4$-	75	54	70	86	38
4h	2-NO_2-C_6H_4-	65	38	77	67	54
4i	3-NO_2 -C_6H_4-	50	45	55	52	75
4j	4-OH-C_6H_4-	65	62	74	77	71
Amoxicillin	-	100	100	100	100	-
Griseofulvin	-	-	-	-	-	100

RESULTS AND DISCUSSION

From the results of antimicrobial data, compounds 4b and 4g were active and compounds 4a, 4e, 4f were moderately active aginst bacterial strain. While 4d, 4i and 4j were shown good activity against A.niger. The structure activity relationship data table, we find that phenyl ring substituted with bromo and amino at 4-position (4b and 4g respectively) shown as excellent result compare to standard drug amoxicillin at a scale of 40ug/ml. While phenyl ring substituted with hydroxy substituted at 4-position not shown antibacterial activity.

ACKNOWLEDGMENTS

Authors are thankful to Department of Chemistry J.J.T University, Jhunjhunu, Rajashthan. Authors are also thankful to Centaur Pharmaceuticals Pvt. Ltd for providing work facilities.

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