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Design-Syntheses, Characterization and Biological Activity Studies of Azobenzen-P,P'-Di(3,1-Benzoxazin-4-One-2yl) and Azobenzen-P,P'-Di[(3-Substituted-4(3h)Quinazolinone-2yl] Derivatives

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Abstract

Sixteen azobenzene-p,p'-di[3-substituted-4(3H)quinazolinone-2yl] were synthesized from reaction of azobenzen-p,p'-di(3,1-benzoaxzin-4-one-2yl) with amino-moieties nucleophlies, like hydrazinehydrate, hydroxylamine, p,toluidine, p-aminobenzene sulphonamide, 2-pyrimidine, 5-nitro-2-aminopyridine, ethyleneamine,5-(p-bromo) phenyl-2-aminothiazol, p,p'-diamino diphenyl sulphone, quinidine hydrochloride, urea, thiourea, 3,5-dimethyl-2-phenyl-4-aminopyrazolin-3-one, N(5-methyl-3-isoxazolyl)-p-aminobenzen sulphonamide, semicarbazide and thiosemicarbazide, in a molar ratio (1:2) respectively. azobenzen-p,p'-di(3,1-benzoaxzin-4-one-2yl), was synthesized by following serial synthetic pathway. Reductive-condensation of p-nitrobenzoic acid in basic media give azobenzen-p,p'-dicarboxylic acid, then treated with thionyl chloride to give azobenzen-p,p'-diacid chloride. It condensed with anthranilic acid to give azobenzen-p,p'-[(dibenzoic acid-2yl)dicarboxamide], upon treatment with thionyl chloride give azobenzen-p,p'-di(3,1-benzoaxzin-4-one-2yl). All synthesized compounds characterized by FTIR, 1HNMR, 13CNMR and mass spectral analyses. All synthesized azobenzen-p,p'-di(3,1-benzoaxzin-4-one-2yl), and sixteen azobenzene-p,p'-di[3-substituted-4(3H)quinazolinone-2yl] compounds, were examined as antibacterial agents against gm(+ve and –ve) bacteria, and antifungal agents. Results showed abroad extended to moderate effects as antibacterial and antifungal agents.

Keywords: Azobenzene; Benzoxazinone; Quinazolinone; Antibacterial; Antifungal

Introduction

2-substituted-3,1-benzoaxzin-4-one derivatives can be considered as semi-acid anhydrides, which undergo many reactions of true acid anhydrides, but at a slower rate [1]. This special reactivity allows these types of heterocyclic compounds to have broad spectrum in medical, biological and industrial fields [1,2]. This class of compounds, found to be useful as antimicrobial [3], anti-platelet aggregation [4], human leukocyte elastase inhibitors [5], receptor agonist active [6], receptor antagonist active [7], enzyme inhibitor [8], protease inhibitor [9-11], fungicidal [12], pesticidal [7]. Also 2-substituted-3,1-benzoaxzin-4-one derivatives, showed some important industrial applications in syntheses of polymeric material [13], optical bleaching agent [14], and cosmetic [15]. On the other hand, they are used as precursors for syntheses of variety of 2,3-disubstituted quinazolin-4-one derivatives [16-19]. Which are known to have medical and biological properties, through reaction with nitrogen nucleophiles [20]. Quinazolinones are class of fused heterocyclic compounds, of two fused benzene and pyrimidinone rings; they are active compounds, exhibiting a broader spectrum of biological activities in animal, as well as in human [21,22]. Literature studies on quinazolinones have shown, that these derivatives possess a wide variety of biological activities, such as antioxidant [23], antifungal [24], antibacterial [25], anticonvulsant [26], anti-inflammatory [27], antihyperlipidemic [28], anticancer [29], antimalarial [30], antispasmodial [31], analgesic [32], antiviral [33], antitubercular [34] and antimicrobial activities [35]. In our work we design syntheses many of di[(3-substituted-4(3H)quinazolinone-2yl] moieties, substituted at (p,p')-position of bridged azobenzene molecule, via di(3,1-benzoxazin-4-one-2yl) moiety, substituted at (p,p')-positions of bridged azobenzene molecule.

Materials and Methods

Synthesis of azobenzene-p,p'-dicarboxylic acid [I]

This compound was obtained by condensation of p-nitrobenzoic acid with itself in basic media in presence of reducing agent like glucose, then upon air-oxidation give azobenzene-p,p'-dicarboxylic acid, yield 48%, m.p. 302, lit. >300°C [36].

Synthesis of azobenzene-p,p'-diacid choride [II]

A mixture of azobenzen-p,p'-dicarboxylic acid (0.27 gm, 0.001mol), excess of thionyl chloride (10 ml), and dry pyridine (3 ml), was refluxed for 2 hours. Reaction mixture was extracted several times with n-hexane, and then rotary evaporated. Resulting residue was washed with dry diethyl ether, recrystallized from petroleum ether to give compound [II]. 0.28 gm, yield 91.2%, m.p. 154°C.

Synthesis of azobenzen-p,p'-[(dibenzoic acid-2yl)di carboxamide] [III]

To a clear stirred solution of azobenzen-p,p'-diacid chloride (0.307 gm, 0.001mol) in dry benzene (50 ml) containing dry pyridine (5 ml), anthranilicacid (0.274 gm, 0.002mol) was added. Reaction mixture

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was stirred for further 5 hours, until completion of reaction which was monitored by TLC, using ethyl acetate: ethanol [2:3] eluent. A precipitate was formed, filtered, washed with distilled water, recrystallized from benzene, to give compound [III]. 0.4 gm, yield 80.7%, m.p. 288-290°C.

Synthesis of azobenzen-p,p'-di[3,1-benzoxazine-4-one-2yl] [IV]

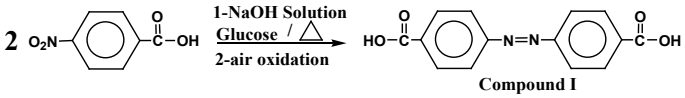
To a clear solution of azobenzen-p,p'-[(dibenzoic acid-2yl) dicarboxamide] (0.508 gm, 0.001mol) in excess of thionyl chloride (10 ml), dry pyridine (5 ml), was reflux for 2 hours, until completion of reaction which was monitored by TLC, using ethyl acetate : ethanol [2:3] eluent. A solid was formed. Reaction mixture was cooled; solid was formed, filtered and washed with dry diethyl ether, recrystallized from DMF, to give compound [IV]. 0.4 gm, yield 84.74%, m.p. 320°C.

Syntheses of azobenzen-p,p'-di[3-substituted-4(3H)-quinazolinone-2yl] [Va-Vp]

A mixture of azobenzen-p,p'-di[3,1-benzoxazine-4-one-2yl] (0.472 gm: 0.001 mol), and amino moieties compounds, like hydrazine hydrate, hydroxylamine hydrochloride, quinidine, urea, thiourea, semicarbazide, thiosemicarbazide, aromatic and hetro-aromatic amines, 1,2-diaminoethane dihydrochloride (0.002 mol) (Table 1) in DMF (25 ml), was refluxed for a time (Table 1), until completion of reactions were monitored by TLC using petroleumether : ethyl acetate [3:2] eluent. Solids were separated, filtered and purified by crystallization from suitable solvents (mentioned in Table 1), to give azobenzen-p,p'-di[3-substituted -4(3H)-quinazolinone-2yl] [Va-Vp].

Discussion

Chemistry of benzoxazine, quinazolin, quinazolinone and their derivatives have much considerable attention, due to effective biological and pharmacological importance. Awing to these reasons, we design to synthesis anew benzoaxazin-4-one and quinazolin-4-one derivatives. We design syntheses many of di[(3-substituted-4(3H)quinazolinone-2yl] moieties, substituted at (p,p')-position of bridged azobenzene molecule, via di(3,1-benzoxazin-4-one-2yl) moiety, substituted at (p,p')-positions of bridged azobenzene molecule, according to the following synthetic routes.

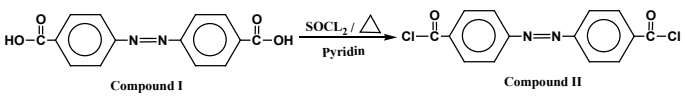


Compound I

Synthesis of azobenzene-p,p'-dicarboxylic acid [I] [36]

This compound was synthesized in by reductive-condensation, then air-oxidation of basic solution of p-nitrobenzoic acid. Characterized by CHN-analysis and FTIR-spectral analysis, CHN-analysis was agreed with theoretical data. FTIR-spectrum of this compound [I], showed stretching bands of (-OH broad), (C=O and N=N) groups at (3437-2544, 1693 and 1693 cm^{-1}) respectively.

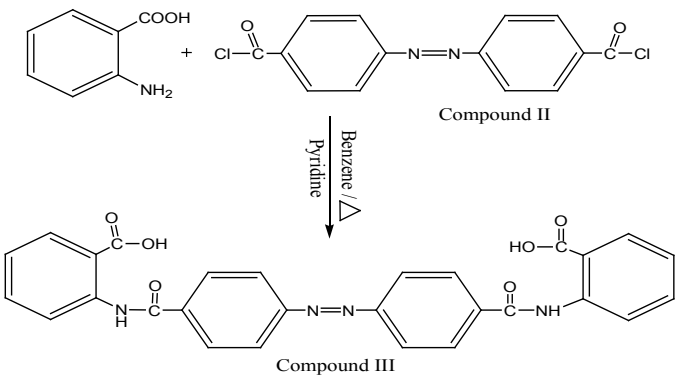
Synthesis of azobenzen-p,p'-diacid chloride [II]



Compound I Compound II

Heating compound [I] with excess of thionyl chloride in presence of pyridine, give good yield of compound [II], which was characterized by CHN- analysis, FTIR, 1H NMR, 13 CNMR and mass spectral analyses. CHN- analysis was agreed with theoretical data. IR-spectrum of this compound [II], showed stretching bonds vibration of C=O and N=N at 1774 and 1577 cm^{-1} respectively. While 1H NMR-spectrum showed only aromatic protons (8H,m) at (7.9 - 8.2) ppm. 13C NMR-spectrum showed C=O and aromatic carbons signals at (166 and 122-134) ppm respectively. Mass spectral analysis showed molecular ion (M+2) and (M+2H)+2 ions at m/z 307 and 309 respectively.

Synthesis of azobenzene-p,p′-[(dibenzoicacid-2yl)dicarboxamide] [III]



Compound II

Compound III

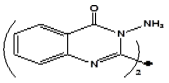
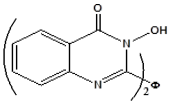
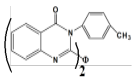
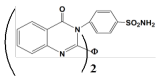
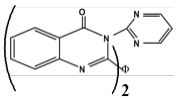
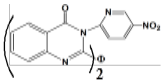
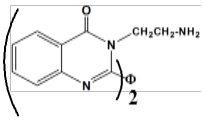
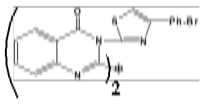
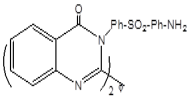
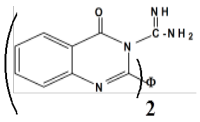
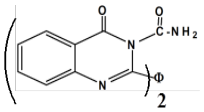
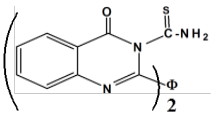
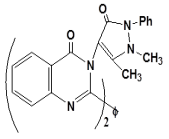
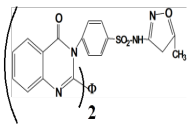
Condensation of compound[II] with anthranilic acid in molar ratio (1:2) in presence of pyridine give compound[III], which was characterized by CHN-analysis, FTIR, 1H NMR, 13C NMR and Mass spectral analysis. CHN- analysis was agreed with calculated data. IR-spectrum showed stretching bands of (OH, NH, C=O, and N=N) groups at 3232, 3309 (broad), 3230, 1676 and 1450 cm^{-1} respectively, beside (C=O), (amide I) and (NH)-bending (amide II) bands at 1608 and 1584 cm^{-1} respectively. While 1H NMR-spectral analysis showed protons of carboxyl as (2H, s) at (12) ppm, amide NH as (2H,s) at (8.6 ppm) and aromatic as (16H,m) at (7.1-8.5) ppm [37]. But ^{13}C NMR-spectrum showed carboxyl and carboxamide carbon as a singlet signals at (169, 164) ppm respectively, beside multiplet signal of aromatic carbons at (120 - 153) ppm. Mass spectrum showed, (M+H)+2 and (M+2H)+2 ions at m/z=(309 and 310) respectively.

Synthesis of azobenzene p,p'-di[3,1-benzoxazine-4-one-2-yl] [IV]

Heating compound [III] with excess of thionyl chloride in presence of pyridine, to give compound [IV], Which was characterized by CHN-analysis, FTIR, 1H NMR, 13C NMR and Mass spectral analysis. CHN-analysis was identical to calculated data. IR-spectrum show C=O cyclic ester), C=N and N=N stretching bands at 1762, 1604, 1570 cm^{-1} respectively. 1H NMR- spectrum showed only aromatic proton as (16H,m) at (7.5-8.5) ppm. While 13C NMR showed C=O (cyclic ester), C=N carbons as singlet signal at (179, 153 ppm), beside multiplet aromatic carbon at (117 - 150) ppm respectively. Mass spectral analysis does not show molecular ion M+2 at m/z (472), but showed fragmented ions m/z (236), probably obtained from molecular ion decomposition with charge is considered to be localized at azo-nitrogen atoms of synthesized molecule of compound [IV] as in the following fragments:

Synthesisofazobenzen-p,p'-di[3-substituted-4(3H)-quinazolinone-2yl][Va-Vp]

Heating compound [IV] with amino-moiety compounds, given in Table 1, in molar ratio (1:2) give azobenzen-p,p'-di[3-substituted-4(3H)-quinazolinone-2yl] [Va-Vp], which were characterized by FTIR-

No	Amino-moieties	Refluxed time	No	Structure formula	Weight of product(gm)	Yield%	Crystallizing solvent
1	Hydrazine hydrate	8 hr	**Va**		0.53	88	DMF
2	Hydroxylammonium chloride	6 hr	**Vb**		0.4	78	DMF
4	p-toluidine	7 hr	**Vc**		0.3	46	DMSO
5	p-Aminobenzenesulphoneamide	8 hr	**Vd**		0.4	51	DMF
6	2-aminopyrimidine	6 hr	**Ve**		0.48	77	DMSO
7	2-amino-5-nitropyridine	8 hr	**Vf**		0.44	61	DMSO
8	1,2-diaminoethanedihydrochloride	6 hr	**Vg**		0.45	81	DMF
9	2-Amino-5(p-bromo)phenyl-1,3-thiazole	7 hr	**Vh**		0.42	49	DMSO
10	4,4'-diaminodiphyenylsulphone	8 hr	**Vi**		0.45	52	DMF
11	Quinidine hydrochloride	5 hr	**Vj**		0.47	85	DMF
12	Urea	5 hr	**Vk**		0.43	77	DMF
13	Thiourea	5 hr	**Vl**		0.42	71	DMSO
14	4-amin-1,5-dimethyl-2-phenyl-3-pyrazolin-5-one(amino antipyrine	10 hr	**Vm**		0.38	46	DMF
15	4-amino-N(5-methyl-3-isoxaly) benzenesulphonamide	10 hr	**Vn**		0.41	43	DMSO

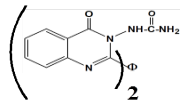
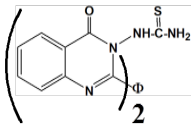
16	Semicarbazide	8 hr	**Vo**		0.4	71	DMF
17	Thiosemicarbazide	8 hr	**Vp**		0.4	69	DMF

Table 1: Reaction of azobenzen-p,p'-di(3,1-benzoaxazin-4-one-2yl)[4], with amino-moieties to give azobenzene-p,p'-di[(3-substituted)-4(3H)quinazolinone-2yl] compounds [5a-5p].

	FTIR V cm^{-1}					^{1}H NMR δ ppm		^{13}C NMR		
No.	**NH_2**	**OH**	**CH Ar.**	**C=O**	**N=N**	**CH Ar.**	**others**	**CH Ar.**	**C=N**	**C=O**
Va	3307-3215	-	3051	1664	1583	7.2-8.1	-	121-153	153	170
Vb	-	3417	3066	1635	1489	6.8-9	10.2 OH	119-131	153	168
Vc	-	-	2929, 3180	1653	1444	6.5-9.2	4.01 CH_3	120-135	153	164
Vd	3464 3236	-	3116	1670	1450	6.5-8.2	9.9 NH_2	112-152	152	179
Ve	-	-	3068	1676	1455	7.2-8.2	-	117-153	153	168
Vf	-	-	3118	1666	1450	-	-	-	-	-
Vg	3433 3213	-	3050	1661	1450	6.3-8.4	4.01 CH_2	111-153	153	164
Vh	-	-	3100	1629	1454	-	-	-	-	-
Vi	3275 3210	-	3116	1666	1446	-	-	-	-	-
Vj	3414 3332 3221	-	3095	1620	1448	6.3-8.8	8.5 NH_2	119-153	153	162
Vk	3367 3217	-	3036	1654	1446	6.2-8.4	8.4 NH_2	120-158	158	161 183
Vl	3367 3174	-	3082	1677	1450	6.2-9.9	8.5 NH_2	110-137	154	162 192
Vm	-	-	2935 2808 3045	1672	1446	-	-	-	-	-
Vn	3226	-	2995 3118	1680	1444	-	-	-	-	-
Vo	3400 3398 3220	-	3178	1670	1450	7.04-8.3	9.9, 10.7 NH &NH2	119-140	153	160 177
V p	3429 3309 3217	-	3101	1670	1469	7.2-8.3	10.5	110-153	153	180 194

Table 2: Physical parameter of Synthesis for azobenzen-p,p'-di[3-substituted-4(3H)-quinazolinone 2yl][Va-Vp].

No.	**Name of compounds**	**Mean of Inhibition zone Diameter (mm)**					
		Staphylococcus aureus	***Bacillus***	***Escherichia coli***	**No. *Klebsiella pneumonia***	***Aspergillus flavus***	***Penicillium***
IV	Azobenzen-p,p'-di[3,1-benzoxazine-4-one-2-yl]	22	-	16	10	13	10
Va	Azobenzen-p,p'-di[3-amino-4(3H) qunazolinone-2yl]	20	17	8	12	12	-
Vb	Azobenzen-p,p'-di[3-hydroxy-4(3H) qunazolinone-2yl]	23	30	8	10	11	13
Vc	Azobenzen-p,p'-di[3,p-touldino-4(3H) qunazolinone-2yl]	17	-	-	11	8	16
Vd	Azobenzen-p,p'-di[3,p-benzenesulfoneamido-4(3H) qunazolinone-2-yl	20	9	8	12	12	25
Ve	Azobenzen-p,p'-di[3,p-pyrimidino-4(3H)qunazolinone-2yl]	8	-	8	8	10	12
Vf	Azobenzen-p,p'-di[3,5'-nitro-2'-pyridin-2'yl-4(3H)qunazolinone-2yl]	9	13	8	8	9	12
Vg	Azobenzen-p,p'-di[3-2'-ethylamino-4(3H)qunazolinone-2yl]	8	8	8	8	-	-
Vh	Azobenzene-p,p'-di[3,4'-p-bromophenyl-2'-(1',3'-thiozolyl)-4(3H) qunazolinone-2yl]	16	15	15	15	11	28
Vi	Azobenzen-p,p'-di[3(p-4'-aminodiphenylsulfone)-4(3H) qunazolinone-2yl]	8	15	8	15	15	16
Vj	Azobenzen-p,p'-di[3-imidino-4(3H) qunazolinone-2yl]	8	11	10	10	-	-
Vk	Azobenzen-p,p'-di[3-carbomido-4(3H) qunazolinone-2yl]	8	8	-	8	-	-

Vl	Azobenzen-p,p'-di[3-thiocarbomido-4(3H)qunazolinone-2yl]	8	13	10	9	12	9
Vm	Azobenzen-p,p'-di[3-(1',5'-dimetyl-2'-phenyl-3'-pyrazolinone)-4(3H) qunazolinone-2yl]	8	15	9	8	-	-
Vn	Azobenzen-p,p'-di[3-(5'-methyl-3'-isoxazolyl)benzenesulfoneamido-4(3H)qunazolinone-2yl]	8	8	8	9	14	9
Vo	Azobenzen-p,p'-di[3,N-ureido- 4(3H) quinazolinone-2yl]	8	14	8	8	12	-
Vp	Azobenzen-p,p'-di[3,N-thioureido-4(3H)quinazolinone-2yl]	8	11	8	9	12	-

Table 3: Antimicrobial activity of compounds [IV-Vp].

spectral analysis, many of them characterized by 1H NMR, 13C NMR, and some of them by mass spectral analyses. IR-spectral analysis of compounds [Va-Vp], showed quinazolin-4-one ring stretching bonds C=O, and C=N, at rang (1680-1620), and (1635-1591) cm^{-1}, azo-group (N=N) stretching bonds at rang (1489-1444) cm^{-1}, as well as to starching of 3-substituted moieties [37] are given in Table 2 [37]. 1H NMR spectrum of compounds [V(a, b, c, g, j, k, l, n, o, p)], showed beside quinazolinone aromatic proton as (16,m) at rang (6.5-9.2) ppm, protons signals of 3-substituted moieties, which were shown in Table 2. 13C NMR- spectral analysis of compounds [V(a, b, c, g, j, k, l, n, o, p)], showed quinazolinone, (aromatic, C=O, C=N) carbon signals at (110-140), (163-180), (152-164) ppm, respectively, beside carbon signals of 3-substituted moieties, which are given in Table 2. Mass spectral analysis of compounds [Va, Vd] showed M+2 ions m/z (500, 780), and [Vb] showed [M-H]+2 ions at m/z (501), compound [Ve] dose not showed (M)+2 ions at m/z (626), but show fragmented ion at m/z (236), probably abstained by decomposition of molecular ion, with charge considered to be localized at azo-nitrigen atoms of this symmetrical compounds to give following fragmented ion:

Anti-microbial study

Synthetic compounds [IV, V(a-p)], were examined as antibacterial agents against gm (+ve) *Staphylococcus aureus*, *Bacillus* bacteria, and gm (-ve) *Escherichia coli*, *Klesbsiella*, *Pneumonia* bacteria, in comparison with effect of Cephalexin, Amoxicillin, Tetracycline Lincomycin antibiotics. Also these compound [IV, V(a-p)], were examined as agents against *Aspergillus flavus* and Penicillium, Fungi in comparison with effect of Nystatine and Fluconazole antifungal treatments. According to the results given in Table 3, following observation would be deduced.

- First: compounds [V(a, b, h, i)], were found to have a broadening effect on gram (+ve) *Bacillus* bacteria in comparison with effect of Cephalexin, Amoxicillin, Tetracycline antibiotitics.
- Second: compounds [V(a, b, c, d)], were found to have moderate to higher antibacterial effect on gram (+ve) *Staphylococcus aureus* bacteria in comparison with effect of Cephalexin, Amoxicillin, and Tetracycline antibiotics.
- Third: compounds [V(a, d, h, i)], were found to have good to excellent antibacterial effect, against gram (-ve) *Klebsilla pneumonia* bacteria, in comparison with effect of Tetracycline antibiotics.
- Fourth: compounds [V(a, d, I, l, n, o, p)], were found to have a moderate to excellent antifungal effect on *Aspergillus fungi* in comparison with the effect of Nystatin and Fluconazole antifungal treatment. But compounds [V(c, d, h, i)], were found to have moderate to excellent antifungal effect on *Penicillium* fungi in comparison with the effect of Nystatin and Fluconazole antifungal treatments.

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