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CHEMISTRY OF NOVEL BIPHENYL IMIDAZOLE-THEIR SYNTHESIS & MICROBIAL EVALUTION

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Abstract:
We are interested in synthesis and developing the chemistry of novel biphenyl imidazole. For this 5-(4'-bromomethyl-biphenyl -2 yl)-2H-tetrazole (TTBB) was treated with the hexaminium salts to give aldehyde (1) which on further treatment with benzoin product & hydroxyl pyralidione to yields the respective biphenyl Imidazole, Oxadiazole (2-4).The structures of the synthesized compounds were confirmed by Physico-chemical test and spectral techniques, representative samples were screened for their antimicrobial activity against gram positive and gram negative bacteria.

Introduction:

The development of simple, facile and efficient methodologies for the synthesisof five-member heterocycles is one of the major challenges in the field of synthetic organic chemistry. Among five-member heterocyle Imidazole, Oxadiazole and pyrazolesrepresent a class of compounds having a great importance. Symmetrical and unsymmetrical1, 3, 4-oxadiazoles are biologically versatile compounds possessing anti-inflammatory[I], antifungal[II],anti-parasitic [V], antimicrobial[VI-VII] and antiviral activities[VIII-X]. The widespread use of 1,3,4-oxadiazoles as a used in medicinal chemistry. Also Imidazole derivatives possess various important in biological properties including fungicidal, herbicidal and plant-growth regulator activities[XI-XII].Some of the compounds exhibit antiviral and anticancer properties.[XIII-XIV]. Substituted imidazole are in the core portion in many bioactive molecules in sartan family such as losartan and olmesartan[XV].They have also been employed in the preparation of ionic liquids[XVI]. Thus, the synthesis of imidazoles is an important task in organic chemistry. Though the preparation of benzimidazoles has recently been studied [XVII-XXIII]

Experimental

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 300 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

General procedure for synthesis of hexaminium salts

The solutionof hexamethylenetetramine (5.86 mmol) in $CHCl_3$ (20 mL) was added drop wise to mixture of 5-(4'-bromomethyl-biphenyl -2 yl)-2H-tetrazole (5.86 mmol) & dry $CHCl_3$ (20 ml).The mixture was refluxed for 30 min to complete precipitation. The precipitate collected by filtration and washed with chloroform and dried in vacuum to give hexaminium salts.

Synthesis of 2'-[2H-tetrazole-5-yl] biphenyl-4-carboaldehyde (1)

A solution of hexaminium salt (0.1g, 0.24 mmol) in 10 ml of ethanol: water (3:2) was refluxed for 24 h. The reaction mixture was cooled and solvent was removed under reduced pressure and then water was added (5 mL). The reaction mixture was extracted by ethyl acetate and dried over$MgSO_4$. The solvent was removed under reduced pressure and crude product was purified by column chromatography to yields the pure aldehyde (1)

B.P. =120-125 °C, yield = 66%IR (cm-1): 1780(C=O), ^{1H} NMR (DMSO-d6, δ/ ppm): 5.32 (s, 1H, NH), 7.12-7.56 (m, 8H, Ar -H), 9.70 (s, 1H, CHO) ^{13}C NMR (DMSO-d6, δ/ ppm): 122-138 (Ar-C), 155(C=N), 190 (CHO)LCMS; m/z: 250; Anal.Calcd for $C_{14}H_{10}N_4O$ C, 67.38 H, 4.66; N, 22.68% Found: C, 67.54, H, 4.69, N,22.05 %

Synthesis of 2-{3-[2'-(2H-tetrazole-5-yl)-biphenyl-4-yl]-[1, 2, 4] oxadiazole-5-yl methyl}-pyralidine-3-one (2)

A mixture of compound **(2)** (1 mole), N-hydroxy-2-3-oxo-pyrrolidin-2yl-acetamidine (1 mole), ammonium acetate (2 mole), &PEG 400 was reflux for 5-6 hr. Progress of reaction was monitor by TLC.Upone completion reaction mass was quench in water. Exact in ethyl acetate, Organic layer was Separated, Concentrated organic layer to get pale yellow oil (2)

B.P=105°C, yield = 77%

IR (cm-1): 1750(C=O), ^{1}H NMR (DMSO-d6, δ/ ppm): 2.10(s, 1H, NH),2.50 (t, 2H, CH_2), 2.80(t,2H,CH2) ,3.40 (d, 2H ,CH2) 3.90 (t ,1H, CH),5.80 (s, 1H,NH), 7.30 -7.60 (m, 8H, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm): 28.42(CH_2), 35(CH_2),39 (CH),70.14 (CH_2), 120-135 (Ar-C), 180(C=O) LCMS; m/z: 388; Anal.Calcd for $C_{34}H_{26}N_4O$ C,62.61; H, 4.16; N, 25.04% Found: C, 61.58; H, 4.66, N, 25.36 %

Synthesis 5-[4'-(5 benzyl-4-phenyl-1H-imidazole-2-yl)-biphenyl-2-yl]-2H-tetrazole (3)

A mixture of compound **(2)** (1 mole), Benzoin product (1 mole), ammonium acetate (2 mole) &PEG 400 was reflux for 5-6 hr. Progress of reaction was monitor by TLC. Upon completion reaction mass was quench in water. Exact in ethyl acetate Organic layer was Separated, Concentrated organic layer to get pale yellow (3)

B.P. =160-165°C, yield = 72 %

IR (cm-1): 1760(C=O ester)^{1}H NMR (DMSO-d6, δ/ ppm): 3.50 (s, 2H ,CH_2),5.70 (s, 1H,NH), 7.10 -7.70 (m, 18H, Ar -H), 9.20 (s,1H, NH),^{13}C NMR (DMSO-d6, δ/ ppm): 29.30(CH_2), 121-134 (Ar-C),156(C=N), LCMS; m/z: 453; Anal.Calcd for $C_{30}H_{23}N_5$ C,79.61; H, 5.16; N, 15.04% Found: C, 78.58; H, 5.66, N, 15.36 %

Synthesis of (4-8)5-[4'-(5 benzyl-1, 4-diphenyl-4, 5-dihydro-1H-imidazole-2-yl)-biphenyl-2-yl]-2H-tetrazole

A mixture of compound **(2)** (1 mole), Benzoin product (1 mole), ammonium acetate (1 mole), aromatic amine (1 mole) &PEG 400 was reflux for 5-6 hr. Progress of reaction was monitor by TLC. Upon completion reaction mass was quench in water. Exact in dichloromethane. Organic layer was Separated, Concentrated organic layer to get pale yellow colored oil (4-8)

Spectral Data for aniline (4a)

5-[4'-(5 benzyl-1, 4-diphenyl-4, 5-dihydro-1H-imidazole-2-yl)-biphenyl-2-yl]-2H-tetrazole

Yield: 66%; b.p. =125-135 °C: IR (cm-1): 1760(C=O ester), ^{1}H NMR (DMSO-d6, δ/ ppm): 2.55 (d, 2H, CH_2), 2.90(m,1H,CH) ,3.50 (d, 1H ,CH), 5.90 (s, 1H,NH), 7.20 -7.60 (m, 23, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm): 38.42(CH_2), 56.56(CH),65 (CH), 120-136 (Ar-C), LCMS; m/z: 532; Anal.Calcd for $C_{35}H_{28}N_6$, C,78.61; H,5.16; N,15.04% Found: C, 79.58; H, 4.66, N, 15.36 %

Spectral Data for 1 metoxy aniline (4b)

5-[4'-(5 benzyl-1metoxy, 4-phenyl-4, 5-dihydro-1H-imidazole-2-yl)-biphenyl-2-yl]-2H-tetrazole

Yield: 78%; b.p. =125-135 °C: IR (cm-1): 1760(C=O ester), ^{1}H NMR (DMSO-d6, δ/ ppm): 2.60 (d, 2H, CH_2), 2.80(m,1H,CH) ,3.40 (d, 1H ,CH),3.80 (s,3H,OCH_3), 5.75 (s, 1H,NH), 7.20 -7.60 (m, 22, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm): 38.42(CH_2),51.47 (OCH_3),56.88(CH),65.65 (CH), 120-136 (Ar-C), LCMS; m/z: 562; Anal.Calcd for $C_{36}H_{30}N_6O$, C,76.61; H, 5.16; N, 14.90% Found: C, 76.58; H, 5.66, N, 15.36 %

Spectral Data for para chloro aniline (4c)

5-[4'-(5 benzyl-1chloro, 4-phenyl-4, 5-dihydro-1H-imidazole-2-yl)-biphenyl-2-yl]-2H-tetrazole

Yield: 80%; b.p. =125-135 °C: IR (cm-1): 1760(C=O ester), ^{1}H NMR (DMSO-d6, δ/ ppm): 2.68 (d, 2H, CH_2), 2.74(m,1H,CH) ,3.47 (d, 1H ,CH), 5.75 (s, 1H,NH), 7.20 -7.60 (m, 22, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm): 35.42(CH_2), 55.00(CH), 65.62(CH), 120-136 (Ar-C), LCMS; m/z: 566; Anal.Calcd for $C_{35}H_{27}N_6ClC$,74.61; H, 4.16; N, 6.04% Found: C, 74.58; H, 4.66, N, 5.36 %

Spectral Data for para methyl aniline (4d)

5-[4'-(5 benzyl-1methyl, 4-phenyl-4, 5-dihydro-1H-imidazole-2-yl)-biphenyl-2-yl]-2H-tetrazole

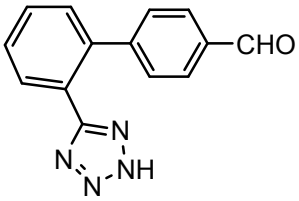
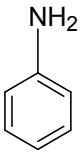
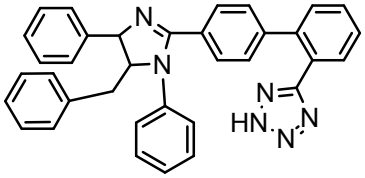
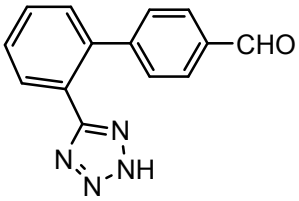
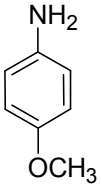
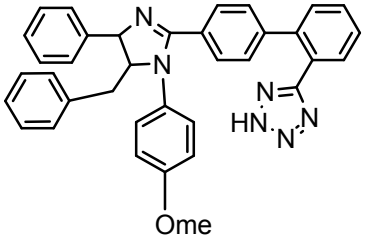
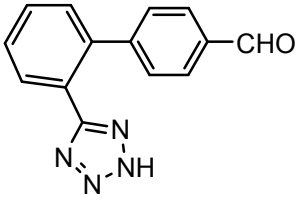
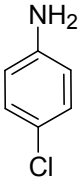
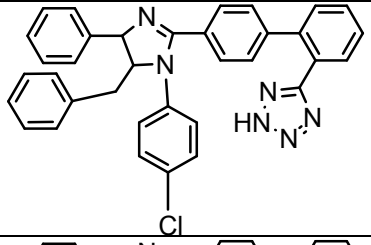
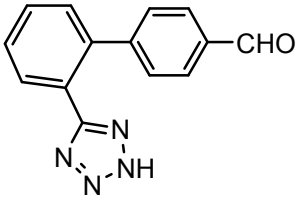
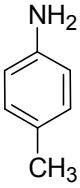
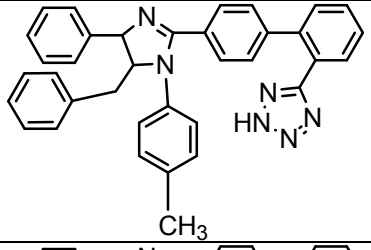
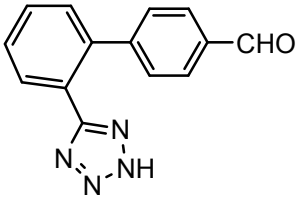
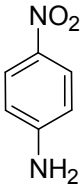
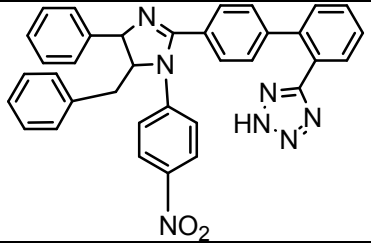
Yield: 78%; b.p. =125-135 °C: IR (cm-1): 1760(C=O ester), ^{1}H NMR (DMSO-d6, δ/ ppm):2.30(s,3H,CH_3), 2.48 (d, 2H, CH_2), 2.65(m,1H,CH) ,3.75 (d, 1H ,CH), 5.85 (s, 1H,NH), 7.20 -7.60 (m, 22, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm): 20(CH_3), 35.42(CH_2), 53..56(CH),62.30 (CH), 121-137 (Ar-C), LCMS; m/z: 548; Anal.Calcd for $C_{36}H_{30}N_6$,C,79.61; H, 5.16; N, 15.04% Found: C, 79.58; H, 5.66, N, 15.36 %

Spectral Data for para nitro aniline (4e)

5-[4'-(5 benzyl-1-nitro, 4-phenyl-4, 5-dihydro-1H-imidazole-2-yl)-biphenyl-2-yl]-2H-tetrazole

Yield: 80%; b.p. =130-135 °C: IR (cm-1): 1766(C=O ester), ^{1}H NMR (DMSO-d6, δ/ ppm): 2.55 (d, 2H, CH_2), 2.70(m,1H,CH) ,3.60 (d, 1H ,CH), 5.85 (s, 1H,NH), 7.22 -7.68 (m, 22, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm): 34.45(CH_2), 56.70(CH),66.84 (CH), 123-137 (Ar-C), LCMS; m/z: 577; Anal.Calcd for $C_{35}H_{27}N_7O_2$,C,72.61; H, 4.16; N, 16.04% Found: C, 71.58; H, 4.66, N, 16.36

Synthesis of 5-substituted 1-aryl 2, 3-diphenyl imidazoles

Sr no	Aldehyde	Amine	Product	Time	Isolated yield
4a				1 hr	85%
4b				1.5 hr	78%
4c				1.8 hr	80%
4d				2.5 hr	78%
4e				3.5 hr	65%

The structures of the products were settled from their spectral (IR, 1H NMR, and MS) and analytical data.

REACTION SCHEME

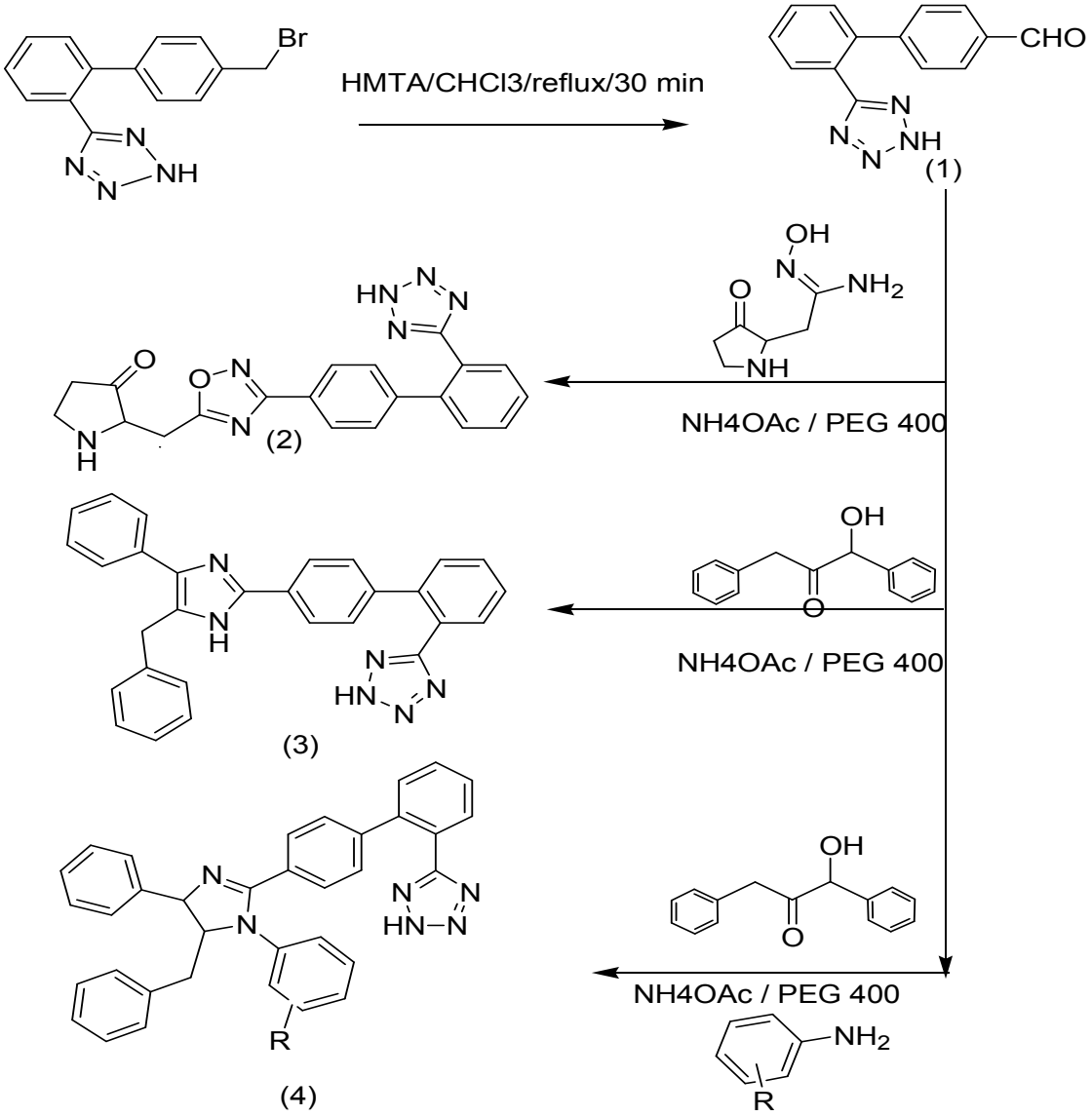


Table I. **Antimicrobial activities of some newly synthesized compounds**

Compds	Inhibition Zone (mm)						
	Gram-negative		Gram-positive		Fungi		Yeast
	E.coli	*P.Putide*	*B.Subtilis*	*S.lactis*	*A.niger*	*P.Sp.*	*C.Albicans*
4a	16	14	19	22	16	9	9
4b	17	15	18	20	19	11	9
4c	16	15	19	18	18	9	8
4d	19	20	20	21	19	11	11
4e	15	14	18	17	18	8	7
DMSO	0	0	0	0	0	0	0
Amphicilin®	23	21	20	22	23	15	15

E.coli. = Escherichia coli; P.Putide = Pseudomonas Putide; B. Subtilis = Bacillus Subtilis; S. lactis = Sterptococcuslactis; A. niger = Aspergillusniger; P. Sp. = PenicilliumSp; C. Albicans = candida Albicans.
The sensitivity of microorganisms to the tested compounds is identified in the following manner*;
Highly Sensitive = Inhibition zone: 15-21 mm
Moderately Sensitive = Inhibition zone: 9-15 mm
Slightly Sensitive = Inhibition zone: 5-8 mm
Not Sensitive = Inhibition zone: 0 mm
* Each result represents the average of triplicate readings.

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