Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

https://doi.org/10.36673/AJRCPS.2024.v12.i01.A03

SYNTHESIS OF AMIDE DERIVATIVES VIA BENZIMIDAZOLES AND EXPLORING BIOEVALUATION

Krishnarao[*1] and M.M.S. Laxmanakumar[1]

[1*]Department of Organic Chemistry, PRISM PG and DG College (Affiliated to Andhra University), Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

In this investigation, the protocol followed by preparation of a novel derivatives of the desired compounds. The compounds (7a-7f) can be obtained from the mixture of 5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-amine (5), substituted aromatic carboxylic acid (6) in the presence of dehydrating agent DCC as a catalyst in ethanol at 700C. The compound (5) can be prepared by the mixture of 1-(2-(4-bromophenyl)-5-methyl-1H-benzo [d] imidazol-1-yl)-2-chloroethan-1-one (4) and thiourea in Toluene and con H2SO4. The compound (4) can be synthesized from 2-(4-chlorophenyl)-1H-benzo[d]imidazole (3) with Chloro acetic acid and triethylamine is base and MDC as solvent at 350C. The 2-(4-chlorophenyl)-1H-benzo [d] imidazole (3) is obtained by the 4-Chloro benzaldehyde (2) and O-phenyl diamine (1) in the presence of $ZrOCl_2$ in ethanol. All the newly obtained derivatives were evaluated by the advanced spectroscopic analysis such as 1HNMR, 13CNMR and LCMS and structural determination of titled analogous were calculated by elemental analysis. In addition to the newly synthesized compounds were examined by their anti-microbial activity.

KEYWORDS

2-(4-chlorophenyl)-1H-benzo [d] imidazole, 1-(2-(4-bromophenyl)-5-methyl-1H-benzo [d] imidazol-1-yl)-2-chloroethan-1-one, Thiosemicarbazide, 1, 3, 4-thiadiazol-2-amine, Substituted aromatic carboxylic acid, DCC and Anti-microbial activity.

Author for Correspondence:
Krishna Rao N,
Department of Organic Chemistry,
PRISM PG and DG College,
Visakhapatnam, Andhra Pradesh, India.

Email: naallakrishnarao@gmail.com

INTRODUCTON

Amide functional group is a main key functional group in organic chemistry and medicinally chemistry and also its widespread occurrence in peptide and non-peptide natural products, therapeutic small molecules and new polymeric materials. The most general route way for synthesizing amides involves the activation of the carboxylic function by means the conversion of

carboxylic acids into the corresponding acid chlorides. After, this reactive derivative is coupled with the suitable amine to yield the corresponding amide. Alternatively, carboxylic acids, by the use of activating reagents, can be transformed into reactive acylating intermediates (acyl chlorides, anhydrides, activated esters) which directly react in situ with the suitable amines without their preliminary isolation and purification.

The biological activity of various molecules containing amide bond such as amiAntitumor[1], kinase inhibitors[2], Anticonvulsant Activity[3], Antifungal Agents[4], cytotoxicity[5,6], Rho-kinase Inhibitory Activity[7], Antimicrobial Activity[8,9], Antioxidant Activity[10], anti-proliferative activity[11], anti-inflammatory[12].

The use of coupling reagents is the only practicable way when the reagents useful for obtaining acid chlorides from carboxylic acids are not compatible with other chemical functions or protecting groups present on the substrate. The use of coupling reagents is the only practicable way when the reagents useful for obtaining acid chlorides from carboxylic acids are not compatible with other chemical functions or protecting groups present on the substrate. The importance of amides has promoted the development of new protocols and reagents based on these approaches and alternative methods for amide bond formation

The direct formation of amide bond by the condensation of non-activated carboxylic acids and primary amine is extremely attractive due to its low environmental impact. The metal-based catalysis was used in direct amide preparation and an alternative to coupling reagents has been reported .The main synthetic catalysts are employed for direct admiration are boronic acids and esters together with Lewis acid metal complexes.

The main focus on the dithiazole amine derivatives are interest moieties in the organic chemistry in recent time and also applied in area of medicinally chemistry as well as pharmaceutical area of chemistry. These derivatives are used as intermediate in drug design in medicinally chemistry. Our continuous program, the synthesis of amide bond molecules formed with various carboxylic acids in the presence dehydrating reagent such as DCC.

METHODS AND MATERIALS

Experimental

All the analytical chemicals and synthetic grade reagents purchased from Fine chemicals and were used without further purification. The reaction progress was monitored by thin layer chromatography. The melting point of the all the newly synthesized compounds were determined open at one end and were uncorrected using an Electrochemical Mk3 apparatus. ^{1}HNMR and ^{13}CNMR spectrum were recorded on 400MHz Bruckner spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilanes (Me4Si) as an internal standard. Molecular mass of the synthesized compound were determined by LCMS spectrometer

2-(4-chlorophenyl)-1H-benzo[d] imidazole

Take dry and clean four neck 50mL RBF and mixture of chlorobenzaldehyde (1.125mmol) was added to a stirred solution of 1, 2-phenylenediamine (1.125mmol) and $ZrOCl_2$ (2.5mmol) in ethanol (25ml) for five minutes at reflux and Stirring was continued for two hours. The progress of the reaction was checked with help of TLC. After completion of the reaction (TLC, eluent Hexane: ethylacetae 5:5), the solvent was removed under reduced pressure and extracted with ethyl acetate three washings and the organic layer was washed with Braine water (25ml). Organic layers were separated and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography using petroleum ether: EtOAc (6:4), which gave desired product as a solid in 94% yield.

1HNMR (400MHz, CDCl3) δppm-12.215 (s, 1H, CONH), 8.207-8.074 (m, 4H, Ar-H), 7.542-7.354 (m, 4H, Ar-H), 13CNMR (100MHz, CDCl3) δppm: 151.44, 140.74, 139.14, 130.21, 128.24, 128.85, 127.85, 127.64, 122.68, 118.37, 116.65, LCMS: 230.42 (M+2); Molecular Formula-C13H9ClN2; Elemental Analysis: Calculated: C-68328, H-3.97, N-12.25: Obtained: C-68.20, H-3.96, N-12.62.

2-(4-chlorophenyl)-1H-benzo [d] imidazole 2-(2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) acetate

2-(4-chlorophenyl)-1H-benzo [d] imidazole 2-(2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) acetate is dissolved in 25mL of methylene dichloride in 50mLfour neck RBF and triethylamine was added .The slowly add the chloroaceticacid lot wise. The total mixture setup on the magnetic stirrer and continued the reaction for 5hrs at reflux. The progress of the reaction was monitored by TLC (5:5 = EtOH: n-hexane). After completion of the reaction, unconsumed chloroacetyl chloride can be evaporated. The completion of the reaction was identified by the TLC and the crude was taken in a ethylacetae and washed with saturated solution of sodium bi carbonate and separated the organic solvent. The organic solvent distilled off under vacuum distillation final compounds obtained.

1HNMR (400MHz, CDCl3) δppm-11.874 (s, 1H, COOH), 8.114-7.842 (m, 4H, Ar-H), 7.612-7.432 (m, 4H, Ar-H),^{13}CNMR (100MHz, $CDCl_3$) δppm: 174.25,153.04, 140.09, 133.21, 130.46, 129.92, 128.92, 128.56, 124.62, 118.45, 112.62, 50.75; LCMS: 288.71 (M+2); Molecular Formula-$C_{15}H_{11}ClN_2O_2$; Elemental Analysis: Calculated: C-62.84, H-3.87, N-9.77: Obtained: C-62.76, H-3.86, N-9.85.

5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-amine

The mixture of 1-(2-(4-bromophenyl)-5-methyl-1H-benzo [d] imidazol-1-yl)-2-chloroethan-1-one and thiourea is dissolved in acetic acid in a clean and dry 50mL RBF. The reaction was continued at 60-70^{o}C.The completion of the reaction was identified by the TLC and the crude was taken in a ethylacetae and washed with saturated solution of sodium bi carbonate and separated the organic solvent. The organic solvent distilled off under vacuum distillation final compounds obtained

^{1}HNMR (400MHz, $CDCl_3$) δppm: 8.135-8.042 (m, 2H, Ar-H), 7.652-7.346 (m, 6H, Ar-H); ^{13}C NMR (100MHz, $CDCl^3$) δppm: 167.24, 160.72, 151.33, 141.65, 136.29, 132.35, 129.06, 128.44, 128.12, 127.95, 124.63, 120.06, 118.45,30.35;;LCMS:342.51(M+2);Molecular Formula-$C_{16}H_{12}ClN_5OS$; Elemental Analysis: Calculated: C-56.22, H-3.54, N-9.20.49: Obtained: C-56.16, H-3.52, N-20.55.

N-(5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-yl) benzamide

The mixture of compound (5) and substituted aromatic carboxylic acid dissolved in MDC in 25ml RBF. The dehydrating agent " DCC " added above mixture and arranged on the hot plate cum magnetic stirrer and continued for two hours at 35^{o}C. The formation desired product was identified by TLC (as mobile phase system – EtOAc: n-hexane = 4:6) and spot visualized in Iodine chamber. If completed the reaction, the solvent would be evaporate and extracted with ethyl acetate. Finally washed with a solution Na_2CO_3, separated the solvent and distilled under vacuumed. The desired product obtained from recrystized from ethanol.

N-(5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl)-2, 3-dihydro-1, 3, 4-thiadiazol-2-yl) benzamide (7a)

^{1}HNMR (400MHz, $CDCl_3$) δppm-12.105 (s, 1H, CONH), 8.210-.132 (m, 4H, Ar-H), 7.694-7.312 (m, 5H, Ar-H), 4.456 (s, 2H, -CH_2); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 166.27, 164.33, 151.65, 149.02, 140.36, 138.25, 133.65, 131.06, 130.57, 129.71, 129.16, 128.85, 128.39, 127.64, 123.68, 119.37, 117.65, 51.66; LCMS – 447.28 (M+2); Molecular Formula-$C_{23}H_{16}N_5S$; Elemental Analysis -Calculated: C-61.95, H-3.62, N-15.71; Obtained: C-61.90, H-3.61, N-15.70;

N-(5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-yl)-4-hydroxybenzamide (7b)

^{1}HNMR (400MHz, $CDCl_3$) δppm-12.096 (s, 1H, CONH), 9.262 (s, 1H, -OH), 8.196-8.056 (m, 2H, Ar-H), 7.684-7.273 (m, 8H, Ar-H), 6.942-6.785 (m, 2H, Ar-H) 4.613 (s, 2H, -CH2); ^{13}CNMR (100 MHz, $CDCl_3$) δppm-167.45, 164.36, 159.05, 152.69, 150.75, 142.03, 135.65, 133.39, 130.34, 128.65, 127.83, 126.45, 124.38, 122.02, 120.04, 118.59, 50.62; LCMS (m/z): 463.72 (M+2) Molecular Formula-$C_{23}H_{16}N_5ClO_2S$; Elemental Analysis -Calculated: C-59.80, H-3.49, N-15.16 Obtained: C-59.72, H-3.47, N-15.25.

N-(5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-yl)-4-methoxybenzamide (7c)

^{1}HNMR (400MHz, $CDCl_3$) δppm-12.194 (s, 1H, CONH), 8.134-7.914 (m, 4H, Ar-H), 7.652-7.115 (m, 8H, Ar-H), 4.574 (s, 2H, -CH2), 3.704 (s, 3H, -OCH_3); 13CNMR (100Hz, CDCl3) δppm- 167.61, 164.09, 162.62, 153.11, 150.04, 137.81, 133.74, 129.21, 128.79, 128.36, 128.06, 127.45, 127.11, 123.05, 120.42, 118.36, 54.82, 51.34; LC-MS– 477.84; Molecular Formula-$C_{24}H_{18}N_5ClO_2S$; Elemental Analysis -Calculated: C-60.57, H-3.81, N-14.71; Obtained: C-60.50, H-3.79, N-14.77.

4-bromo-N-(5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl)-1, 3, 4-thia diazol-2-yl) benzamide (7d)

1HNMR (400MHz, $CDCl_3$) δppm-12.105 (s, 1H, CONH), 8.210-7.132 (m, 4H, Ar-H), 7.694-7.312 (m, 5H, Ar-H), 4.456 (s, 2H, -CH2); 13CNMR (100MHz, CDCl3) δppm-166.27, 164.33, 151.65, 149.02, 140.36, 138.25, 133.65, 131.06, 130.57, 129.71, 129.16, 128.85, 128.39, 127.64, 123.68, 119.37, 117.65, 51.66; LC-MS: 447.28 (M+2); Molecular Formula-$C_{23}H_{16}N_5S$; Elemental Analysis -Calculated: C-61.95, H-3.62, N-15.71; Obtained: C-61.90, H-3.61, N-15.70.

N-(5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-yl)-4-cyanobenzamide (7e)

1HNMR (400MHz, $CDCl_3$) δppm: 12.241 (s, 1H, CONH), 8.324-7.851 (m, 4H, Ar-H), 7.647-7.345 (m, 5H, Ar-H), 4.517 (s, 2H, -CH_2); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 167.27, 163.33, 152.65, 148.14, 141.85, 137.96, 134.06, 131.88, 130.15, 129.88, 128.97, 128.54, 128.21, 127.57, 123.77, 119.03, 117.66, 52.66; LCMS: 472.65 (M+2); Molecular Formula-$C_{24}H_{15}N_5S$; Elemental Analysis: Calculated: C-61.21, H-3.21, N-17.85; Obtained: C-61.12, H-3.20, N-17.92.

N-(5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-yl)-4-nitrobenzamide (7f)

^{1}HNMR (400MHz, $CDCl_3$) δppm : 12.278 (s, 1H, CONH), 8.421-8.124 (m, 2H, Ar-H), 7.804-7.325 (m, 8H, Ar-H), 7.197-7.012 (m, 2H, Ar-H), 4.857 (s, 2H, -CH_2)]; ^{13}CNMR (100MHz, $CDCl_3$) δppm: 169.14, 165.87, 160.05, 153.78, 149.75, 142.66, 136.17, 134.85, 131.85, 129.74, 127.15, 126.55, 124.78, 122.47, 121.75, 119.59, 51.62; LCMS: 492.28 (M+H); Molecular Formula-$C_{23}H_{15}N_6ClO_3S$; Elemental Analysis -Calculated: C-56.27, H-3.08, N-17.12; Obtained: C-56.33, H-3.06, N-17.18.

RESULTS AND DISCUSSION

In this investigation, the synthesis of N-(5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-yl) benzamide was mediated by DCC is dehydrating agent in a ethanol, as reported in reports titled derivatives. The result and discussion of titled derivatives can be divided.

Synthesis

In this investigation, the protocol followed by preparation of a novel derivatives of the desired compounds. The compounds (7a-7f) can be obtained from the mixture of 5-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl)methyl)-1, 3, 4-thiadiazol-2-amine (5), substituted aromatic carboxylic acid (6) in the presence of dehydrating agent DCC as a catalyst in ethanol at 700C. The compound (5) can be prepared by the mixture of 1-(2-(4-bromophenyl)-5-methyl-1H-benzo [d] imidazol-1-yl)-2-chloroethan-1-one (4) and thiourea in Toluene and con H_2SO_4. The compound (4) can be synthesized from 2-(4-chlorophenyl)-1H-benzo [d] imidazole (3) with Chloro acetic acid and triethylamine is base and MDC as solvent at 350C. The 2-(4-chlorophenyl)-1H-benzo [d] imidazole (3) is obtained by the 4-Chloro benzaldehyde (2) and O-phenyl diamine (1) in the presence of $ZrOCl_2$ in ethanol (Scheme No.1).

Optimization of admiration reaction conditions was performed by choosing substituted benzoic acid as model substrate. The reaction was previously investigated under catalytic conditions. Our result was particularly good and interesting, as the product was recovered pure in short times and in excellent yield without requiring the use of complex purification procedures. Encouraged by the success of this preliminary study, the adopted procedure was applied for the preparation of a series of N-phenyl amides. Different alkyl and aryl carboxylic

acids were tested under the developed reaction conditions using aniline, the amine component, as a constant (Scheme No.1).

The maximum yield of the compounds obtained in presence of dicyclohexyl carbodiimde (DCC) catalyst than oxidative related catalyst such as sulphuric acid (H2SO4), phosphorus pentoxide (PCl5), Polyphosphoric acid (PPA) and dicyclohexyl carbodiimde (DCC) whereas various amount of catalyst utilized during the reaction (Table No.1).

The various solvents were used during the reaction that were evaluated (DMF, acetonitrile, ethanol, methanol) in the model reaction. It was identified to be the best medium for the reaction, with 94% product yield and therefore used as the solvent for subsequent reactions on the merits of higher yield, green nature and easy work-up.

Biological activity

Anti-bacterial activity

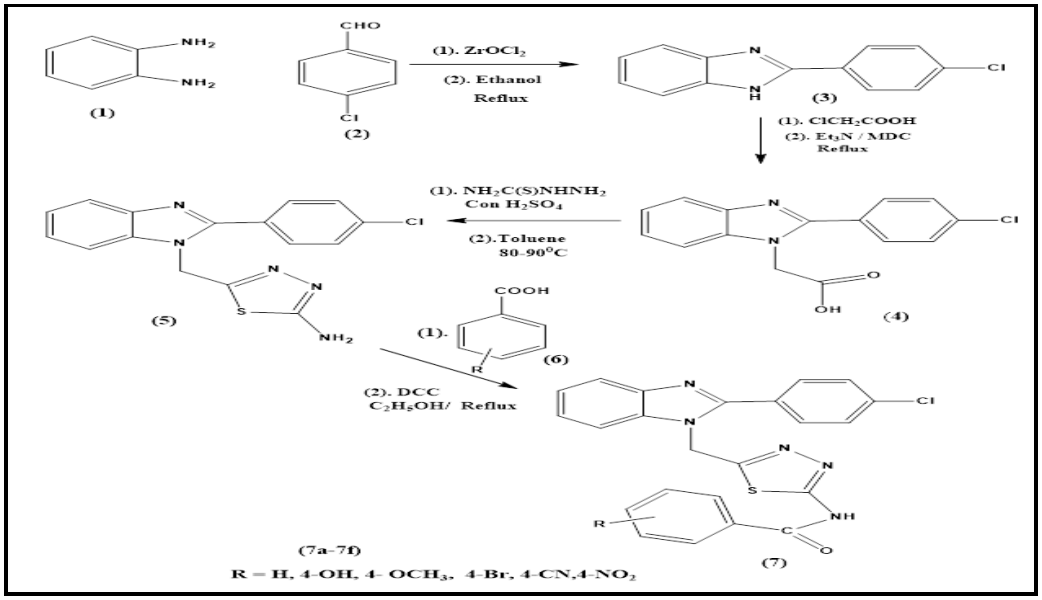
The anti-bacterial activities of new derivatives were examined against 4 pathogenic bacteria strains. The gram negative bacteria screened were *E. coli, P. aeruginosa*. The gram positive bacteria screened were S-aureas and Bacillus.

The desired derivatives were used at the concentration of 250µglml and 500µglml using DMSO as a solvent the streptomycin 10µglml disc were used as a standard drug. The reaming of the derivatives was identified to be moderate active against the tested microorganism. The result of antibiotic activity studies for the compounds as shown in Table No.1.

Anti-fungal activity

Anti-fungal activities of newly derivatives compounds were examined by disc diffusion method against the organism of aspergillusniger and Candida albicans. Compared were treated at the concentrations of 500µglml and 100µglml using DMSO as a solvent. The standard drug was used as ketoconazole 50µglml against both organisms

All the desired compounds were evaluated by anti-bacterial activity as well as antifungal. Activity the electron withdrawing group of compounds and electron releasing group compounds exhibited different potent activities against bacterial as well as fungal strains. Therefore, electron withdrawing group of compounds showed low biological potent activity compared with electron releasing groups. All halogen compounds exhibit well to excellent activity. The compound which possess electron donating group showed moderate activity as shown in Table No.3.



Scheme No.1

Table No.1: The reaction of aryl carboxylic acid and compound -4 (7b)

Entry	Catalyst	Time (hrs)	Yield (%)
1	H_2SO_4	8	57
2	PCl5	8	72
3	PPA	8	69
4	DCC	8	94

Table No.2: The reaction of aryl carboxylic acid and compound -4 (7b)

Entry	Catalyst	Time (hrs)	Yield (%)
1	DMF	8	40
2	CH_3CN	8	65
3	EtOH	8	94
4	MeOH	8	61

Table No.3: Antimicrobial activity screening activity synthesized scaffold

S.No	Compound Code	*Zone of inhibition in (mm)					
		Bacteria				Fungi	
		S.aureus	***E.coli***	***S. typhi***	***B.substill***	***A. Niger***	***C. albicans***
1	3a	04	06	08	06	05	05
2	3b	14	15	13	15	06	07
3	3c	20	19	15	18	14	12
4	3d	18	20	20	19	15	16
5	3e	12	11	13	11	10	09
6	3f	10	12	09	10	08	06
7	Streptomycin	25	25	22	22	NA	NA
8	Ketoconazole	NA	NA	NA	NA	20	20
9	DMSO	---	----	---	---	---	---

CONCLUSION

The structure of the newly synthesized derivatives was elucidated on the basis of elemental analysis and spectral data. When all analysis results of the synthesized compounds were examined, the presence of characteristic peaks proving the formation of imine was observed and the synthesis of the compounds was successful. Also, this synthesis has quite environmentally friendly synthesis method because ethanol and methane Sulphonic acid as a catalyst was used as solvent.

ACKNOWLEDGEMENT

The authors gratefully acknowledge to the management of PRISM PG and DG College Visakhapatnam, India, for laboratory support. The authors also gratefully thank both referees for their helpful critical suggestions.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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Please cite this article in press as: Krishna Rao N and Laxmanakumar. Synthesis of amide derivatives via benzimidazoles and exploring bio-evaluation, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences*, 12(1), 2024, 13-19.