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BENZOXAZINE ANALOGUE CONTAINING 1,2,3-TRIAZOL MOIETY WHICH BEHAVES AS A NOVEL CLASS OF ANTIMICROBIAL AGENT

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ABSTRACT
Benzoxazine and its compounds are frequently used as acceptable configurations for the building of biologically active composites in organic conflation for erecting artificial composites. This prelude condensed summary about the compounds which need to be noticed to have antimicrobial, antimycobacterial, anti-diabetic, anti-hypolipidemic, and anti-depressant properties. It could be a useful tool for pharmacists to discover additional benzoxazine derivatives that are more efficacious and safer. The benzoxazine shell's versatility, as well as its chemical simplicity and availability, make it one of the most promising sources of bioactive composites. Our ideal is to incorporate the aromatic halves in a single patch containing benzoxazine, triazole in the thirst that it'll enhance the natural exertion of the performing composites. The new composites were synthesised in high yield, and all synthesised composites will be thoroughly characterised using precise spectral investigations such as ^{1}H NMR, mass, ^{13}C NMR and IR. All synthesized composites will be screened for their in vitro antibacterial and antifungal exertion following Cup- plate system against standard medicines Ciprofloxacin for bacteria and Miconazole for fungi.

KEYWORDS: Benzoxazine, Heterocyclic Moiety, Cup-plate method, IR, ^{1}H NMR, ^{13}C NMR, Mass Spectroscopy.

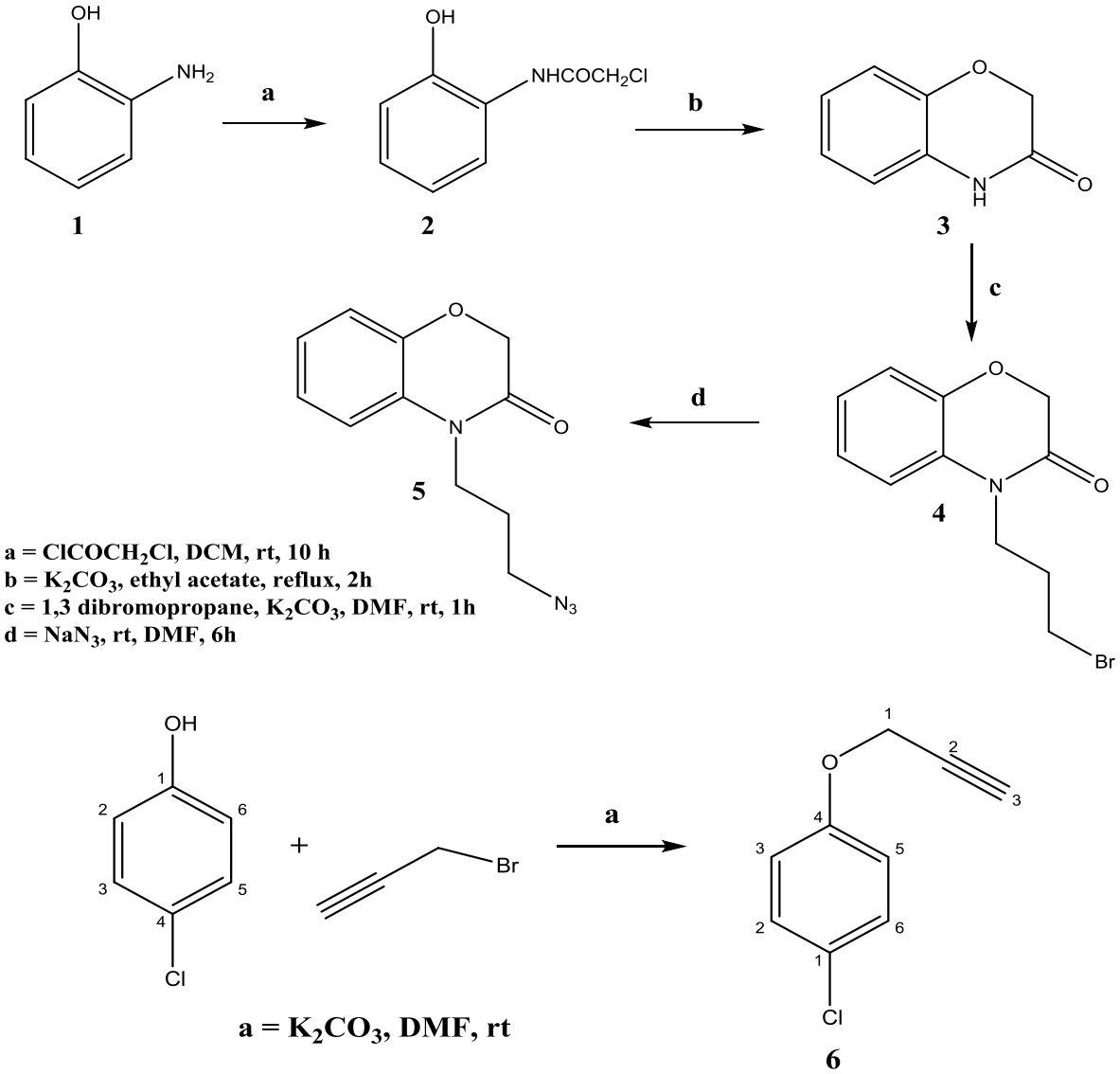
INTRODUCTION
Benzoxazine and its derivatives are frequently used as acceptable configurations for the formulation of biologically active emulsions in organic conflation for erecting artificial composites. This prelude condensed summary about the compounds which need to be noticed to have antimicrobial, antimycobacterial, anti-diabetic, anti-hypolipidemic, and anti-depressant properties. "The versatility of the benzoxazine shell, in addition to its relative chemical simplicity and availability, makes these chemicals amongst the most promising sources of bioactive composites. This has led to the discovery of a wide variety of composites that are of great interest from the point of view of anti-microbial, anti-mycobacterial, anti-diabetic and anti-depressant goods".[1] "Benzoxazine came in the spotlight when the first reclusion of-dihydroxy-2H (4H)-one (DIBOA)[2] and-dihydroxy benzoxazin-3 (4H)-one (DIMBOA)[3] were reported". These composites have been also reclused from roots and upstanding corridor of sludge factory. It was observed that these composites can be further used for the conflation of potent toxic and fungicidal composites. "Fringuelli et. al.[4] have synthesized 6-(1-(4-chlorophenoxy)-2-(1*H*-imidazol-1-yl) ethyl)-4-methyl-2*H*-benzo[b][1,4] oxazin-3(4*H*)-one and estimated their anti-bacterial and anti-fungal exertion in vitro against gram-ve bacteria, gram +ve bacteria and colorful pathogenic strains Candida albicans ATCC 10231,C. glabrata DSM 6425 and C. tropicalis DSM 1346". New ethyl derivations were synthesized by Alper-Hayta et. al.[5] These composites were tested against various gramme +ve bacteria, and some other species in a two-fold periodical dilution pattern. Some compounds of benzoxazine displayed high affections for the 5-HT1A/ 1B/ 1D receptors and inhibit the potent serotonin reuptake. It's a suitable seeker for further evaluation in vivo with the objective of finding more effective anti-depressant agents.[6] Emulsion (Z) dichlorophenethyl-oxazin-3-one derivative has been developed as potent impediments of PI3Kc in enzymatic and cell grounded assays. This emulsion was latterly penciled in vivo a sterile peritonitis model of seditious cell migration and has also shown significant inhibition of neutrophil and monocyte migration to the infected area.[7] "Polucci et. al.[8] did the medicinal chemistry manipulation which led to the discovery of emulsion as potent and picky impediments of VCP ATPase with IC50 of 24 nM and retain anti-proliferative exertion in the sub micro molar range (IC50 = 0.38 μM on HCT-116 cell lines). This represents a first step towards a new class of implicit anti-cancer agents". Hou et al.[9] created a variety of 1,2,4-triazoles and calculated their anti-tumor activity. Apoptosis and western-spot assay results revealed that 1,2,4-triazoles composites are most effective for cancer

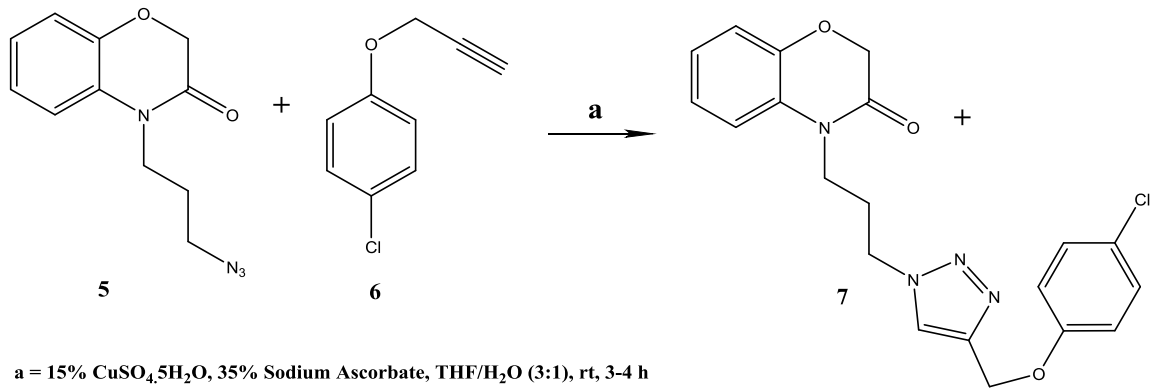
cell and against MetAP2. Cancer outgrowth was found to be largely effective on lung (GI50 = 0.06 M), ovarian, and renal cell lines by Formagio et al.[10] in 2008. Shiradkar et al.[11] developed a new class of triazolyl thiophene compounds that inhibit cdk5/p25. Based on the findings of the SAR investigations, these composites were shown to be the most promising for lowering brain cdk5/p25 levels, and hence have implications for Alzheimer's disease treatment. Poly-benzoxazines, a brand-new class of thermosets, have piqued the interest of both academic and industrial groups due to their superior properties.[12-14] Poly-benzoxazine has won numerous interests in digital packaging, the aerospace industry, composite fabricating, coatings and different fields.[15-18]

EXPERIMENTAL

To make our target compounds, we first made benzoxazine by reacting commercially available 2-aminophenol **(1)** with $ClCH_2COCl$ in Di-chloro methane at normal temperature to produce an intermediate **(2),** which was then treated with $K_2CO_3/CH_3COOC_2H_5$ under refluxing conditions to produce benzoxazine **(3).** The produced compound was refined using chromatographic column to get mono bromo product after N-alkylation of benzoxazine with 1,3 dibromo propane in the presence of K_2CO_3 in DMF **(4).** To obtain the necessary azido compound **(5),** the bromo compound was reacted with NaN_3 in DMF. The alkynes of aromatic compound **(6)** were then produced independently in DMF solvent by reacting 4-chloro phenol with propargyl bromide in the presence of K_2CO_3. Finally, the alkyne (6) was reacted with azido compound **(5)** in presence of $CuSO_4.5H_2O$ and $C_6H_7O_6Na$ to construct 1,2,3-triazole analogues **(7).**

Scheme





a = 15% $CuSO_4.5H_2O$, 35% Sodium Ascorbate, THF/H_2O (3:1), rt, 3-4 h

The above pharmacological important moiety *viz.* benzoxazine and 1,2,3-triazole with aromatic nucleus hooked with alkyl chain in a single molecular frame to obtain compounds having varied and enhanced biological activity. As a result of extensive spectral analysis such as Infra-Red, Mass, Hydrogen-1-NMR and Carbon-13-NMR, the aforesaid synthesised molecule was fully characterized. Using the Cup-plate method, the synthesised chemical was tested for antibacterial and antifungal activity in vitro against reference medicines Ciprofloxacin for bacteria and Miconazole for fungus.

General procedure for the synthesis of alkynes (6)

For 15-20 minutes, the corresponding aromatic moiety (1 mmol) was mixed in DMF with anhydrous K_2CO_3 (3 mmol) at normal temperature. The compounds used in the reaction were then mixed with propargyl bromide (1 mmol). The reaction mixture was agitated until it was complete, which was monitored by TLC. To obtain the corresponding alkynes, the mixture obtained from the reaction was put over chilled ice and the precipitate separated out was sieved through filter paper. The mass spectra of alkyne (TOF ES MS+) validated its formation. The molecule **(6)** is chloro, oxy-prop-2-yl derivative of benzene as shown in the above scheme, TOF ES+ m/z (%): 166 (M+), according to the mass spectrum.

Table I.

S.No	Sample Code	Gram positive Bacteria			Gram negative Bacteria				Fungus			
		S.aureus	*B.subtilis*	*S.epidermis*	*K.pneumoniae*	*S.typhi*	*P.aeruginosa*	*E.coli*	*A.niger*	*A.fumigatus*	*A.flavus*	*C.albicans*
1.	Std.	**21**	**20**	**19**	**24**	**24**	**30**	**22**	**30**	**22**	**22**	**22**
2.	**7**	**18**	13	12	13	14	18	**17**	16	13	14	13

Procedure to synthesise triazole moiety (7)

To a vigorously stirred solution of the azide (1 equivalent) in THF: H_2O (3:1) (6 ml), the synthesized alkynes (1 equivalent) was added separately. $CuSO_4.5H_2O$ (15%) and sodium ascorbate (15%) were added to start the reaction (35 %). The resulting-coloured suspension was swirled for 3-4 hours at room temperature. TLC was used to track the reaction's progress. After the reaction was completed, the aqueous layer was extracted three times with ethyl acetate using ice cold water. The combined organic extract was dried, evaporated under reduced pressure, or filtered using a suction pump to get crude product, that was then allowed to move through (60-120 mesh) silica gel column to yield pure 1,2,3-triazole.

Spectral Analysis of Compound (7)

The light brown solid **(7)** was obtained by combining chloro, oxy-prop-2-yl derivative of benzene **(6)** (0.070 g, 0.35 mmol) with azido compound **(5)** (0.104 g, 0.35 mmol) according to the above-mentioned general technique. Rf = 0.41 in methanol/chloroform (98:2) as system solvent developer. Yield: 0.134 g (79%)

- **IR (KBr) ν_{max}:** 3255, 3051, 2936, 1697, 1481, 1403, 1372, 1245, 1055, 937, 845, 662 cm^{-1}.
- **^{1}H Nuclear Magnetic Resonance (δ, $CDCl_3$, 400 MHz):** 7.56 (s, 1H, *J* = 7.8 Hz), 7.39 (d, 2H, *J* = 7.9 Hz), 7.10 (d, 1H, *J* = 7.85 Hz), 7.01-6.91 (m, 4H), 5.21 (s, 2H), 4.78 (s, 2H), 4.44 (t, 2H), 4.09 (t, 2H), 2.46 (p, 2H).
- **^{13}C NMR (δ, $CDCl_3$, 100 MHz):** 164.1, 157.3, 145.2, 142.9, 130.8, 130.5, 128.1, 128.8, 128.1, 126.4, 120.8, 117.9, 117.7, 117.4, 112.7, 72.1, 67.6, 49.4, 40.4, 26.3.
- **Mass spectra as Time-of-flight mass spectrometry *m/z* (%):** 398 (M^++1).
- **Molecular formula:** $C_{20}H_{19}ClN_4O_3$.

On the basis of above spectral data, compound **(7)** was identified as 4-(3-(4-((4-chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)-2H-benzo[b][1,4]oxazin-3(4H)-one.

RESULTS AND DISCUSSION

In our comprehensive plan to develop a new triazole compound, we have synthesized a novel compound **(7)** using molecular modification approach. The compound

(**5**), had been reported as the main intermediate in this approach, which, when combined with another substance **(6)** in the presence of $C_6H_7O_6Na$ and copper sulphate pentahydrate yielded the desired molecules **(7)**. The Mass, ^1H NMR, IR and ^{13}C NMR were used to completely describe the synthesised chemical and its intermediate.

Antimicrobial and Antifungal Activity

The antibacterial activity of the produced compound **(7)** was tested in vitro at 100g/mL using the cup plate method.

The detailed analysis as shown in the above Table-I proved that the tested compound showed moderate antibacterial activity against P. aeruginosa, K. pneumoniae, B. subtilis, S. typhi , A. fumigatus, S. epidermis, A. niger, A. flavus and C. albicans however they showed substantial antibacterial activity against E. coli and S. aureus.

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