ijlpr 2023; doi 10.22376/ijlpr.2023.13.6.P1-P11

International Journal of Life science and Pharma Research

ISSN 2250-0480

Research Article

Anti-Alzheimer's and Anti-Fungal of Quinoline

Anti-Alzheimer's and Anti-Fungal Activities of Pyrrolo[1,2-*a*] Quinoline Derivatives

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Abstract: Psychiatrists have described the protein deposits in the brain that causes various diseases such as cerebral, functional, physiological dysfunction, and neurodegenerative diseases. Although Alzheimer's disease is detectable, its treatment remains unattainable. More than 4.6 million new patients are recorded yearly, who are affected by Alzheimer's disease and only a few drugs are currently in use for treatment with side effects. Hence, there is a clinical need for new drugs, design, and development. On the other hand, despite the development of antifungal therapeutics over the last three decades, antifungal resistance is still a major cause. Regularly using inappropriate antimicrobials has become a major healthcare problem globally in the 21st century and has been titled a "silent tsunami facing modern medicine." It has been estimated that over 8,000,000 die yearly, which provides scope for developing novel antifungal drugs. In this research paper, we describe the synthesized dimethyl-1-(4-substituted benzoyl)-5-methylpyrrolo[1,2-*a*] quinoline-2,3-dicarboxylate 1a-c and ethyl-1-(4-substituted benzoyl) 5-methylpyrrolo[1,2-*a*] quinoline-3-carboxylate 1d-f were evaluated for *in vitro* antifungal and anti-Alzheimer's activities. The derivatives1a-f were obtained by 1,3-dipolar cycloaddition reaction by treating quaternary salt with dimethyl acetylene dicarboxylate and ethyl propiolate respectively, in the presence of K_2CO_3 and DMF as a solvent. Among all compounds, 1a, 1d, and 1e showed the highest inhibitory capacity with IC_{50} values of 0.28, 0.32, and 0.30 µM, respectively. On the other hand, derivatives were also screened for antifungal activity that displayed moderate activity, whereas 1a and 1f derivatives showed good activity.

Keywords- Alzheimer's, dipolarophile, dimethyl acetylene dicarboxylate, neurologic, physiological dysfunction, ethyl propiolate, psychiatrists.

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Received On 8 February, 2023

Revised On 24 May, 2023

Accepted On 5 June, 2023

Published On 1 November, 2023

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Pramod N Patil, Vijayakumar Uppar, Basavaraj Padmashali and Rangappa Keri , Anti-Alzheimer's and Anti-Fungal Activities of Pyrrolo[1,2-a] Quinoline Derivatives.(2023).Int. J. Life Sci. Pharma Res.13(6), P1-P11 http://dx.doi.org/10.22376/ijlpr.2023.13.6.P1-P11

1. INTRODUCTION

Alzheimer's disease, named after German psychiatrist Alois Alzheimer in the year 1906, is a neurodegenerative disease that is the main cause of dementia and is characterized by critical cerebral, functional, and physiological dysfunction and is rapidly becoming one of the most expensive, lethal, and burdening diseases of this era [1-3]. The report suggests that it is the most common neurodegenerative disease, with more than 50 million cases worldwide; according to the estimates, the number is expected to double every five years and is projected to reach 152 million by the year 2050. Despite the numerous drugs that have been approved, their expected benefits are modest for Alzheimer's disease; the disease persistently remains the same robbing millions of memories and human lives[4-7]. There are 200 or more under development and 75 drugs in clinical trials. Currently, there are 200 drugs in development and 75 undergoing clinical trials. The world faces the same problem with fungal infections in the present scenario. At the start of the 20th century, the bacterial pandemic was worldwide and an important cause of fatality [8-10]. In contrast, fungal infection was not almost taken into consideration. In the late 1960s, when the antibiotic drug was developed, an extreme rise in fungal infection was observed [11,12]. It causes nosocomial fungal infections in patients, particularly on a mucosal surface of the skin, vagina, mouth, and intestine in patients suffering from invasive candidiasis as well as systemically colonizes the bloodstream in candidemia patients and poses a major medicinal challenge in medically and immune-compromised patients, with a mortality rate of 30–45%[13]. These infections are caused by two types of microorganisms; primary and opportunistic pathogens. Despite the development of new therapeutic strategies, there are only mere drugs to fight against invasive fungal infections, and only such polyenes, echinocandins, and azoles are used to treat fungal infections[15]. Hence there is an urge for the discovery of new antifungal therapeutic. In this article, an effort has been made to develop new antifungal and anti-Alzheimer drugs. The research was focused on N-fused heterocyclic compounds that are more important in the synthetic and pharmaceutical industries; the report suggested that Daly and his team, in 1977, isolated perhydropyrrolo[1,2-*a*] quinoline from secretions of the frog Dendrobrates histrionics and *Dendrobrates histrionics* are known to have antibacterial, antifungal, and antitumor activities[15]. For instance, the recent publication of pyrrolo[1,2-a] quinoline and pyrrolo[1,2-a] isoquinoline has shown numerous potential biological activities, which include antioxidant, antimicrobial, anti-inflammatory, anticancer, and antituberculosis activities [16-23]. In previous work, we have described a novel synthetic approach to pyrrolo[1,2-*a*] quinoline derivatives as an interesting larvicidal activity against *Anopheles arabiensis* and the cytotoxicity and antimycobacterial properties in which the selected derivatives exhibited good results[24]. We were sparked to use pyrrolo[1,2-*a*] quinoline as a template for the design of anti-fungal and anti-Alzheimer's therapies.

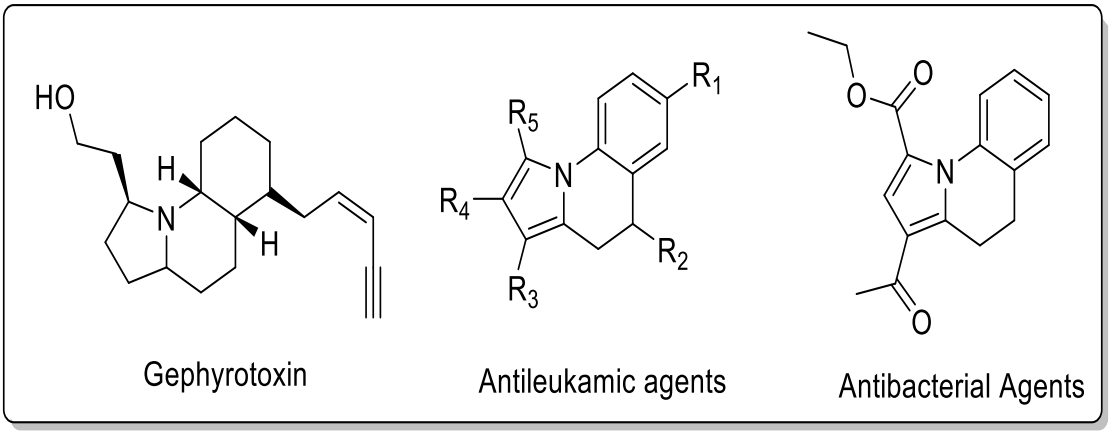


Fig 1: A few derivatives of pyrrolo[1,2-*a*] quinoline-containing natural products and drugs. For example, Gephyrotoxin was studied for its biological activity, and these compounds can act as muscarinic antagonists and exhibit an array of neurological activities.

2. MATERIALS AND METHODS

Melting points were recorded in the Thiele melting point apparatus in an open capillary and were uncorrected. IR spectra were recorded on a Thermo Fisher Scientific FTIR spectrophotometer, NMR spectra, and ^{13}C NMR spectra were recorded with $CDCl_3$ using a Bruker AV 800 spectrometer. Chemical shifts were expressed in δ ppm and were referenced with TMS as an internal standard. The anti-bacterial study of pyrrolo[1,2-*a*] quinoline was performed by disc diffusion method using *C. albicans* as a strain and brain heart infusion agar as a media for the proposed protocol [25] (The clinical microbiology procedures handbook, 1, 1992). The enzymatic activity TcAChE was measured using an adaptation of the previously described method with modification proposed by (Asha M. et al.) [26,27].

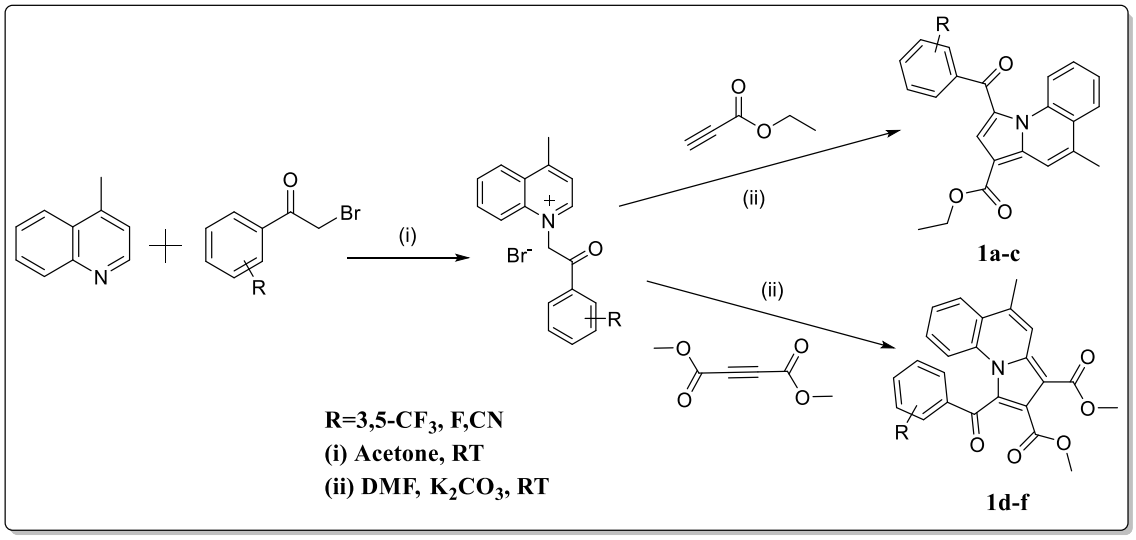


Fig 2: Scheme 1: Synthetic scheme for the preparation of dimethyl-1-(4-substituted benzoyl)-5-methylpyrrolo[1,2-*a*] quinoline-2,3-dicarboxylate1(a-c) and ethyl-1-(4-substituted benzoyl)-5-methyl pyrrole [1,2-*a*] quinoline-3-carboxylate1(d-f).

2.1. Experimental

The moieties 1a-c and 1d-f had been synthesized by treating quaternary salts with different alkynes, such as ethyl propiolate (i) and dimethyl acetylene dicarboxylate (ii), in the presence of K_2CO_3 as base and DMF as a solvent to yield the desired product. The quaternary salt was prepared by treating 4-methyl quinoline with different substituted phenacyl bromide respectively, in the presence of acetone as a solvent to form excellent yields. The pyrrolo[1,2-a]quinolines 1a-f were synthesized by a two-step reaction as shown in Scheme-1 and have been reported in our earlier research paper [24].

2.2. Biological activities

In our previous work, the pyrrolo[1,2-a]quinolines were studied for their larvicidal activity against *Anopheles arabiensis*, and the cytotoxicity and antimycobacterial properties of this pyrrolo [1,2-*a*]quinoline are obtained by molecular target and molecular docking studies. Figure-3 shows the structure of reported biologically active pyrrolo[1,2-*a*]quinoline derivatives. The reported compounds possessed attractive pharmacological recognition. To put more light on these derivatives and their biological impact, in this present work, we screened this pyrrolo [1,2-*a*]quinoline derivatives for anti-Alzheimer's activity and anti-fungal activity against *Candida albicans*.

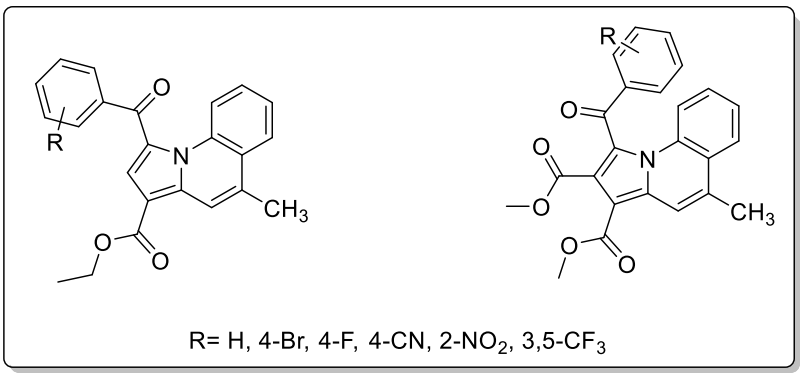


Fig 3: Analogues tested for anti-tuberculosis (TB) activity against the H37Rv strain.

The tested moieties emerged as the most promising anti-TB compound against MDR strains of *Mycobacterium tuberculosis*. *In vitro*, cytotoxicity evaluation of selected derivatives confirmed the safety of the compounds up to 250 µg/mL.

2.3. In vitro anti-Alzheimer's assay

The enzymatic activity TcAChE was measured using an adaptation of the method proposed by Asha M. et al. [27]. The assay solution contained 374 µL of HEPES buffer (50 mM and pH 8.0), a variable volume (10–50 µL) of the stock solution of each compound in methanol (1 mg/mL), 25 µL of AChE stock solution, and the necessary amount of methanol to attain 0.925 mL of the sample mixture in a 1 mL cuvette. The samples were left to incubate for 15 min, and then 75 µL of acetylthiocholine iodide (AChI) solution (16 mM) and 476 µL of DTNB (3 mM) were added. The reaction was monitored for 5 min at 40 nm. Assays were run with a blank containing all the components except AChE, which was replaced by the HEPES buffer. The velocities of

the reaction and the enzyme activity were calculated. A control reaction was carried out using the sample solvent (methanol) without any tested compound, and it was considered 100% activity. The following Eqn calculated the percentage inhibition of the enzyme activity due to increasing test compound concentration.

$$3.\%I = 100 - \left(\frac{V_i}{V_0} \times 100\right) \qquad (3)$$

Where v_i is the initial reaction rate in the presence of an inhibitor and v_0 is the initial rate of the control reaction. The inhibition curves were obtained by plotting the percentage of enzymatic
inhibition versus inhibitor concentration and a calibration curve was obtained from which the linear regression parameters were obtained.

$$IC_{50} = \left(\frac{50-b}{m}\right) \qquad (4)$$

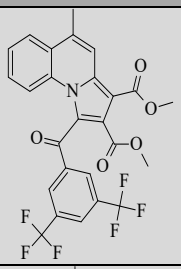
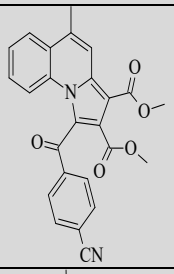
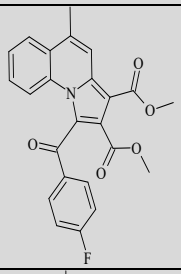
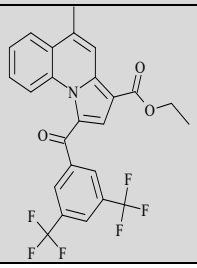
Where b is the interception in the y-axis and m is the slope. The statistical analysis was performed in Microsoft Office Excel[26, 27].

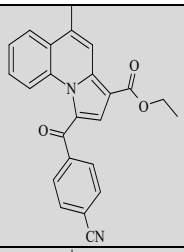
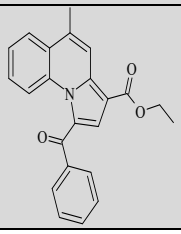
2.4. Disc diffusion antifungal assay

The anti-bacterial study of pyrrolo[1,2-*a*] quinoline was performed by disc diffusion method using *C. albicans* as a strain and brain heart infusion agar as a media. The plates were preserved according to standard method [25]. The stock solution was prepared using 10 mg of the compound in 1 mL of DMSO. Adding compounds into a plate has been done using different concentrations of compounds such as 75 µL, 50 µL, 25 µL, 10 µL, and 5 µL. The plates were then incubated at 37 ^{0}C for 18-24 hr. to know the activity.

3. RESULTS

Table-1: Physiochemical characteristics of pyrrolo[1,2-a]quinoline derivatives (1a-1f)

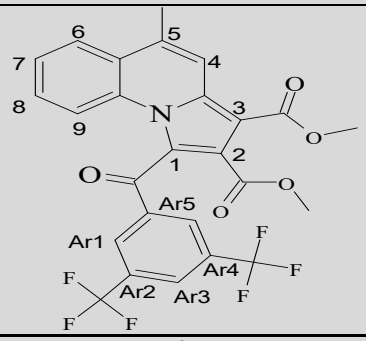
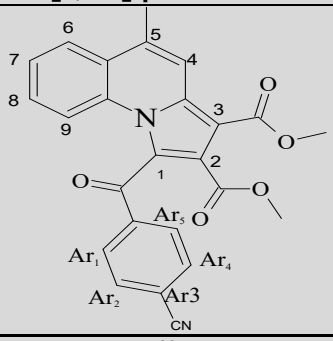
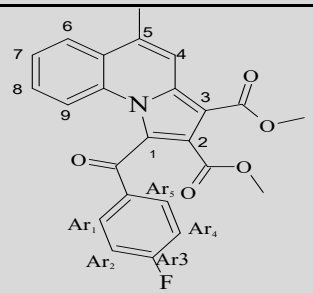
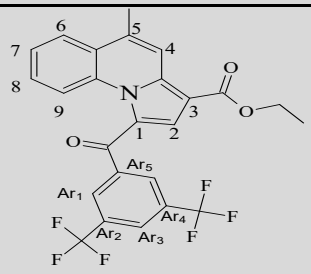
Comp	Structure	Melting Point in$^\circ C$	Yield Reported	Molecular Formulae/ Molecular Weight	Found%(cald) C	H	N
1a		188-189	66.5%	$C_{26}H_{17}F_6NO_5$ (537.4)	58.08% (58.11%)	3.10% (3.19%)	2.57% (2.61%)
1b		184-185	66.7%	$C_{25}H_{18}N_2O_5$ (426.4)	70.36% (70.42%)	4.21% (4.25%)	6.52% (6.57%)
1c		196-197	63.9%	$C_{24}H_{18}FNO_5$ (419.4)	68.67% (68.73%)	4.29% (4.33%)	3.30% (3.34%)
1d		174-175	53.7%	$C_{25}H_{17}F_6NO_3$ (493.4)	60.83 (60.86%)	3.42% (3.47%)	2.80% (2.84%)

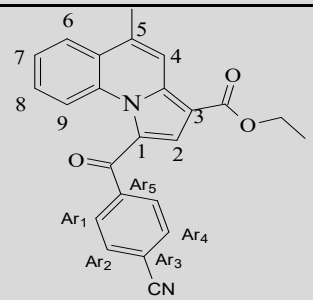
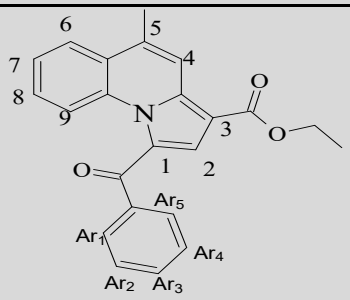
1e 	179-180	50.5%	$C_{24}H_{18}N_2O_3$ (382.4)	75.33% (75.38%)	4.70% (4.74%)	7.29% (7.33%)
1f 	$C_{23}H_{19}NO_3$ (357.4)	58.9%	$C_{23}H_{19}NO_3$ (357.4)	77.25% (77.29%)	5.32% (5.36%)	3.89% (3.92%)

3.1. ^{1}H NMR studies of 1a-f

The formation of product 1a has been elucidated by ^{1}H NMR spectra wherein aromatic protons appeared between δ 8.55 and δ 7.54, and two sharp singlet peaks appeared at δ 3.92 and δ 3.45, indicating the methoxy group and a singlet peak at 2.75 indicating CH_3 peak. The product 1f has been elucidated by ^{1}H NMR spectra in which aromatic peaks appeared between δ 8.15-δ 7.16, a triplet peak at δ 1.58- δ 1.52 indicating CH_2CH_3 and a singlet peak at δ 2.73. The remaining moieties 1b, 1c, 1d, and 1e have been characterized below.

Table 2 :Characterisation data of pyrrolo[1,2-*a*]quinoline derivatives

	
1a	1b
δ 8.55(2H, s, Ar_2, Ar_6), 8.21(1H, s, Ar_4), 8.19(1H, s, H_4), 8.02-8.01(1H, m, H_9), 7.67-7.66(1H, m, H_6) 7.58-7.54(2H, m, H_7, H_8) 3.92(3H, s, OCH_3), 3.45(3H, s, OCH_3), 2.75(3H, s, CH_3).	8.22(1H, d, H_9), 8.21-8.19(2H, m, Ar_3, Ar_5), 7.78(1H, s, H_4), 7.61-7.71 (2H, m, Ar_2, Ar_6), 7.51-7.47(3H, m, H_6, H_7, H_8) 3.93(3H, s, OCH_3), 3.49(3H, s, OCH_3), 2.72(3H, s, CH_3).
	
1c	1d
δ =8.15(1H, d, H_9), 8.10-7.92(2H, m, Ar_3, Ar_5), 7.65-7.45(4H, m, H_4, H_6, H_7, H_8), 7.19-7.16(2H, s, Ar_2, Ar_6), 3.92(3H, s, OCH_3), 3.52(3H, s, OCH_3), 2.70(3H, s, CH_3).	Δ =8.03(1H, s, H_2), 8.02-8.01(1H, m, H_9), 7.66(1H, m, H_6), 7.66 (1H, s, Ar_4), 7.65(1H, s, H_4), 7.63-7.58(2H, m, H_7, H_8), 4.42-4.38(2H, q, H_2)

	2.76(3H, s, CH_3) 1.42-1.40(3H, s, CH_3).
	
1e	**1f**
δ =8.30(1H, s, H_9), 8.14-8.12(2H, m, Ar_3), 8.01(1H, s, H_2), 7.88-7.87(2H, m, H_4, H_6), 7.65, 7.59(2H, m, H_4, Ar_2, Ar_6), 7.58-7.57(2H, m, H_7, H_8), 4.41-4.37(2H, q, CH_2) 2.75(3H, s, CH_3) 1.42-1.40(3H, s, CH_2 CH_3).	δ =8.25(1H, s, H_2), 8.18-8.10(3H, m, H9, Ar_3,Ar_5), 8.01-8.00(1H, m, H_4), 7.90-7.89(1H, m, ArH_4), 7.68, 7.53(4H, m, Ar_2, Ar_6, H_6, H_7, H_8), 4.40-4.37(2H, q, CH_2) 2.75(3H, s, CH_3) 1.58-1.27(3H, s, CH_2 CH_3).

3.2. FT-IR measurements

Table 3: IR-Data of pyrrolo[1,2-a]quinoline derivatives 1a-1f

CODE	(Ar-C-H)	Ester group	C=O
1a	2982	1743	1706
1b	2957	1737	1703
1c	2956	1737	1704
1d	2980	1709	1709
1e	2957	1703	1703
1f	2980	1700	1700

Strong IR absorptions observed in the range 1743-1700cm^{-1} are due to ester carbonyls, and the 1700-1710 cm^{-1} band indicates (C=O) for the derivatives 1a-1f. For1a; FT-IR (neat cm^{-1}); 2982, 1785, 1780, 1743, 1706, 1650, 1620, 1b 2957, 2232, 1737, 1703, 1646, 1535, 1c, 2956, 1737, 1704, 1643, 1598, 1d 1785, 1780, 1709, 1639, 1e 2957, 2228, 1703, 1629, 1542, 1f 2980, 1700, 1634, 1465.

3.3. Pharmacological Studies

3.4. Anti-Alzheimer's activity

Table 4: *In vitro* activities toward AChE inhibition

Code	AChE Inhib[a] IC_{50}(μM)±SD
1a	0.28±0.04
1b	0. 32±0.05
1c	0. 51±0.04
1d	0. 54±0.02
1e	0. 60±0.02
1f	0.30±0.04
Tacrine (std)	0.34±0.02

[a]The values are the mean of five independent experiments ± SD

The biological potential of the synthesized pyrrolo[1,2-*a*] quinoline moieties were screened for anti-Alzheimer's activity. Among all hybrid, compounds 1a, 1d, and 1e showed the highest inhibitory capacity with IC_{50} values 0.28, 0.32, and 0.30 μM, respectively, compared with parent drug tacrine (IC_{50}=0.34 μM). The remaining compounds (1b, 1c, and 1f) showed good to moderate AChE inhibition (IC_{50}=0.51-0.60 μM).

3.5. Antifungal activity against Calbicans with disc diffusion method

Table:5 Minimum inhibitory concentrations of pyrrolo[1,2-*a*] quinoline derivatives against *C. albicans*.

Sample	*C. albicans*			Fluconazole
	75µl/mL	50µl/mL	25µl/mL	
1a	24	19	19	45
1b	23	21	19	50
1c	25	20	18	>40
1d	23	20	20	35
1e	26	19	19	35
1f	25	18	18	40

S – Sensitive, R – Resistant Standard values for disc diffusion

The values are the mean of five independent experiments ± SD.
1) Fluconazole (30 µg): C. albicans - 24mm.

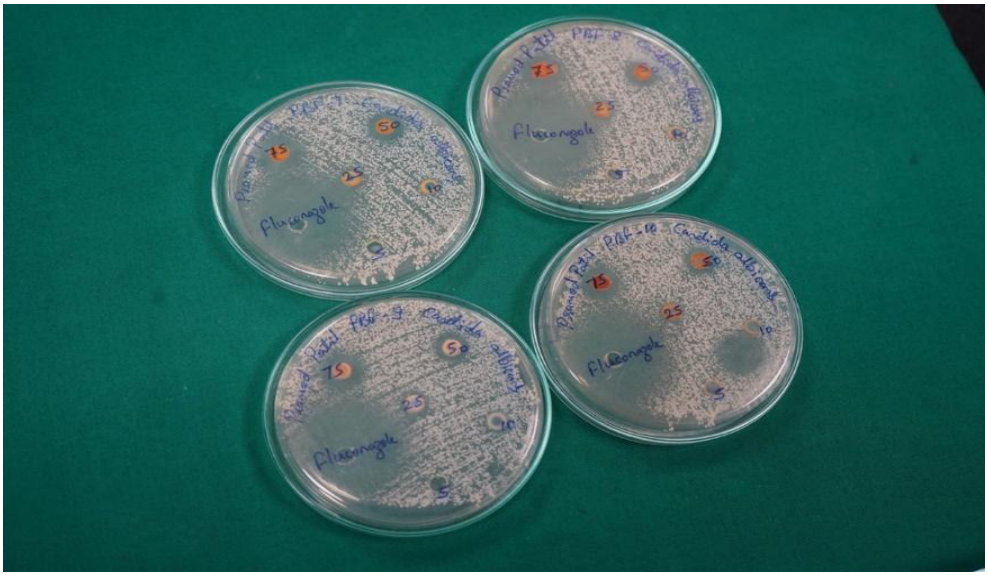


Fig 4: Inhibition zone of *C.albicans* from pyrrolo[1,2-*a*]quinoline derivatives.

The biological potential of the synthesized pyrrolo[1,2-*a*] quinoline moieties were screened for antibacterial properties by the disc diffusion method; the plates were preserved according to the standard method was performed by disc diffusion method using *C. albicans* as a strain, and brain heart infusion agar as a media. Fluconazole was used as a reference standard, and derivatives were added in different concentrations of compounds such as 75, 50, 25, 10, and 5 µL/mL. The stock solution was prepared using 10 mg of a compound in 1 mL of DMSO. Adding compound into a plate have been done using different concentrations of compounds such as 75, 50, 25, 10, and 5 µL/mL. The plates were then incubated at 37 ^{0}C for 18-24 hr. to know the activity. The results at concentrations 10 µL/mL and 5 µL/mL have shown only mere resistivity, while at concentrations 75, 50, and 25 µL/mL have shown moderate to good results.

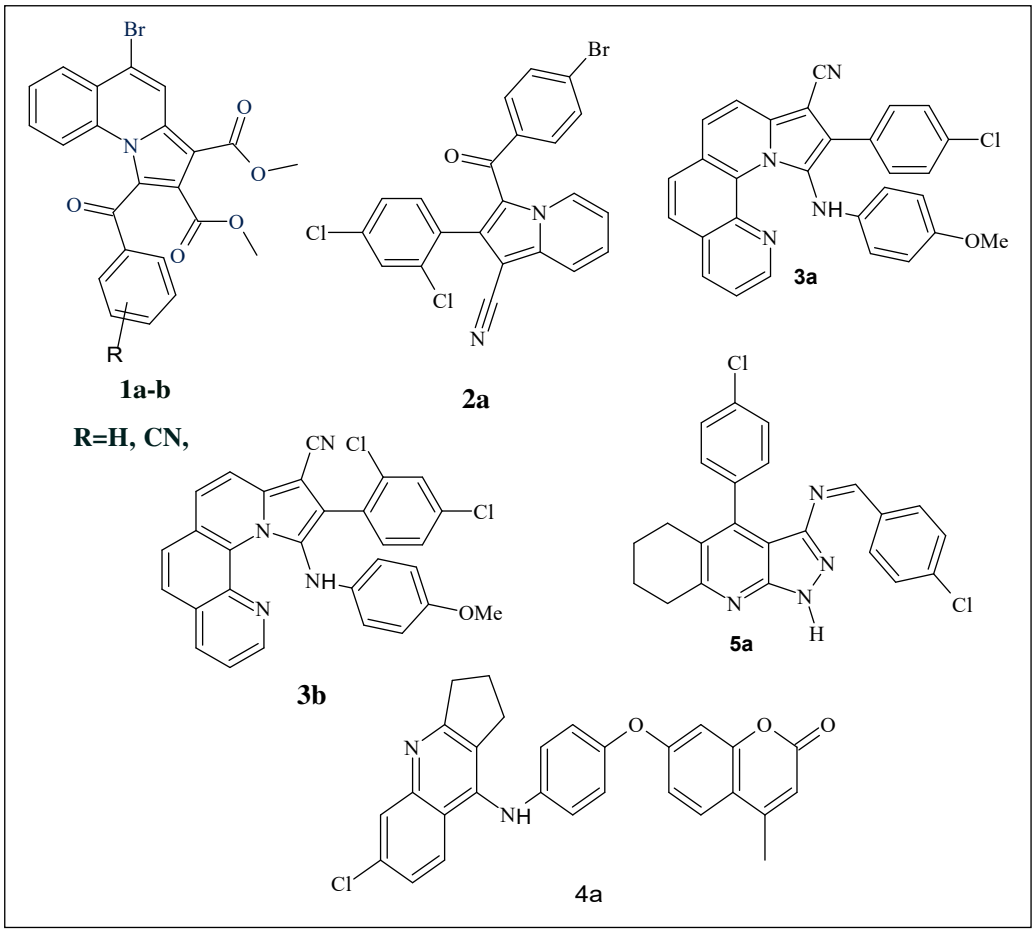


Fig. 5: Analogues tested for anti-fungal for various strains, anti-Alzheimer's activity inhibitory activity against AChE, and the IC50 value with reference standard tacrine.

4. DISCUSSION

Based on our previous research, the pyrrolo quinoline derivatives have shown promising results in cytotoxicity, antimycobacterial, and larvicidal activity against *Anopheles arabiensis*[28]. It made us think of investigating them for anti-Alzheimer's and anti-fungal activity. Recent research has suggested that N-benzo-fused homologous derivatives have exhibited good results in this area. It would be interesting to evaluate these compounds in anticipation that the investigation will lead to the discovery of novel compounds with potential therapeutic applications. The reported articles suggested that pyrrolo[1,2-a] quinoline derivatives have the potential to be effective drug targets for the treatment of fungal infections; *in vitro* screening of these derivatives showed varying degrees of inhibitory potential against *C. albicans*, with derivatives 1a-b demonstrating the highest inhibitory[28-30]. Literature indicated that several compounds had been tested for anti-fungal activity against various species of standard strains such as *Candida*, *Aspergillus*, *Cryptococcus*, and *performance*, out of which derivative 2a exhibited the best fungal activities against *Aspergillus*. However, none of the derivatives showed anti-fungal activity against Cryptococcus performance. Only 2a exhibited anti-fungal activity among various derivatives against *C. candida* and *Aspergillus* species [31]. Compound [4-(6-Chloro-2-(*p*-tolyl oxy)quinolin-3-yl)methyl]-2-(4-methoxyphenyl)-2*H*-1,2,4-triazol-3(4*H*)-one and compound [4-(2-(2-Methoxyphenoxy)quinolin-3-yl)methyl]-2-(4-methoxyphenyl)-2*H*-1,2,4-triazol-3(4*H*)-one, have shown good anti-fungal activity against reference standard *C.albicans*[32,33]. Desai, Isaivani, and Mostafa have used the agar disc diffusion method to perform the anti-fungal activity of compounds 3a and 3b with p-fluro and p-choro phenyl substitution against C. *albicans* (ATCC66027). Erythromycin, Oxacillin, and ketoconazole were used as reference standards. The result indicated that both compounds exhibited more potency against fungal activity than the standard drugs. 3a and 3b could be potential candidates for treating anti-fungal infections [34]. Compound, 10-(3,5-dimethoxy phenyl)-11-((4-chlorophenyl) amino) pyrrolo[1, 2-a][1, 10] phenanthroline-9-carbonitrile has shown good potential against *C. albicans* using the agar disc diffusion method, erythromycin, and ketoconazole were used as reference standards [35,36.] The literature survey narrates that N-benzo fused homologous derivatives showed moderate potency in inhabiting AChE, with Compound 4a showing significant anti-AChE activity with an IC_{50} of 16.17µM compared to the reference drug rivastigmine (IC_{50}=11.07 µM)[38-40]. Compound 4a contained a 4-methyl chrome none unit for peripheral site interaction and a quinoline unit for catalytic site binding [38-40]. The 2-(p-tolyl)- 5,6,7,8-tetrahydrofuro[2,3-b] quinolin-4-amine exhibited the highest level of inhibition in the furotacrine group, with IC_{50} values of 2.9±0.4 µM and 119±15 µM for eqBuChE and hBuChE, respectively[41]. Although several derivatives were synthesized and tested for their AChE inhibitory activity, N-(-4-chlorobenzylidene)-4-(4-chlorophenyl)-5,6,7,8-tetrahydro1H-pyrazolo[3,4-b] quinoline-3-amine 5a, showed almost twice the inhibitory activity of tacrine *in vitro* [42-44.] The most potent derivatives against AChE and BChE were identified through an *in vitro* assay. The compound 7-Chloro-N-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl) methyl)-1,2,3,4-tetrahydroacridin-9-amine exhibited an IC_{50} value of 0.521 µM against AChE, while the compound N-((1-(4-

methoxybenzyl)-1H-1,2,3-triazol-4-yl) methyl)- 1,2,3,4-tetrahydroacridin-9-amine showed an IC_{50} value of 0.0521 µM against BChE[45-47]. Our synthesized compounds have exhibited significant anti-fungal and ani-Alzheimer's activity which shows that incorporating N-benzo fused homologous derivative skeleton can lead to a promising strategy to develop novel and potent therapeutic agents for diseases.

5. CONCLUSION

The synthesized ethyl-1-(substituted benzoyl) - methylpyrrolo[1,2-*a*] quinoline-3-carboxylate(1a-c) and ethyl-1-(5substitutedbenzoyl)-5-methylpyrrolo[1,2-*a*] quinoline-2,3-dicarboxylate 1d-f were evaluated for *in vitro* antifungal activity against *c. albican* strain and anti-Alzheimer's. Among all hybrid, compounds 1a, 1d, and 1e showed the highest inhibitory capacity with IC_{50} values 0.28, 0.32, and 0.30 µM, respectively, compared with parent drug tacrine (IC_{50}=0.34 µM). The remaining compounds 1b, 1c, and 1f showed good to moderate AChE inhibition (IC_{50}=0.51-0.60 µM). The SAR study reveals the substituents with fluorine at the benzene ring 1a, 1d, and 1e inhibit excellent AChE inhibition activity. However, all these newly developed hybrids showed improved AChE inhibition compared to the parent drug tacrine. Altogether the newly synthesized hybrids appear promising anti-AD compounds, acting as good AChE inhibitors. The derivatives screened for antifungal activity displayed moderate activity, exhibiting the range between 12 µL/mL-15 µL/mL for 75-fold compared to the standard antifungal fluconazole. At the same time, 1a and 1f derivatives showed good activity compared to the leftover derivatives possessing inhibitory activity lesser than the standard.

6. ACKNOWLEDGEMENT

We thank Rani Channamma University, Belagavi, for providing laboratory facilities.

7. AUTHORS CONTRIBUTION STATEMENT

Basavaraj Padmashali conceptualized the synthesis design, and Rangappa Keri performed the biological activities. Vijayakumar Uppar and Pramod Patil conducted the synthesis and analyzed the data, and necessary inputs were given for designing the manuscript. Finally, all the authors discussed the methodology and contributed to the final manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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