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Research Article

Synthesis and Biological Evaluation of Some Novel Quinoline Derivatives Bearing Pyrazole Moiety

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ABSTRACT

Reported herein are the design, development and investigation for antibacterial and antifungal studies of a novel series of substituted quinoline analogues bearing pyrazole moiety. Acetanilide derivatives were prepared from the reaction of various anilines with acetyl chloride. Cyclization of these acetanilide derivatives (Vilsmeier-Haack reaction) using phosphorus oxychloride and dimethyl formamide afforded corresponding 2-chloroquinoline-3-carbaldehyde compounds(1a-1l). Titled molecules were synthesized through treatment of 1a-1l with hydrazine hydrate to afford corresponding 1H- pyrazolo [3,4-b] quinolines (2a-2l). All the synthesized analogues were recrystallized and characterized through FTIR, ^{1}H-NMR and mass spectroscopy. All analogues were screened for antibacterial activity against gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) bacteria while antifungal activity against *Candia albicans*, and *Aspergillus niger* by disc diffusion method. Compounds 2c, 2e, 2h, 2k, and 2l exhibited promising antibacterial and antifungal activity when compared with standard drugs ciprofloxacin and fluconazole, respectively. Thus, these studies suggest that quinoline derivatives bearing pyrazole moiety are interesting scaffolds for the development of novel antibacterial and antifungal agents.

INTRODUCTION

In recent years, the number of life-threatening infections arising from gram-positive, gram-negative bacteria and fungi has risen exponentially. These are considered one of the serious health concerns globally in 21st century. Rapidly evolving drug-resistant pathogens consequences in a dramatic decrease in the efficacy of presently available treatments.[1] According to a 2021 report, antimicrobial resistance leads to the death of one million people worldwide every year and the figure is expected to rise to ten million by 2050.[2] Furthermore, fungal infections endanger human health, particularlyin immunocompromised patients.[3,4] *Candida* and *Aspergillus* species cause more than 90% of life-threatening invasive fungal infections (IFI).[5] *C. albicans* are the most frequent cause of IFI and the fourth foremost cause of infection of nosocomial bloodstream in hospitals, with a mortality rate of approximately 40%.[6] The discovery of novel antibacterial and antifungal drugs is a significant task in deterring these serious medical problems. Consequently, synthesizing a novel category of antimicrobial agents with distinct molecular frameworks and mechanisms involved is essential as a replacement or alternative for existing antibiotics. In recent decades, many researchers have focused on introducing new chemotherapeutics that can overcome acquired resistance through novel targets and structure-based drug design.[7-10]

The chemistry of heterocyclic molecules has become one of the most important scientific disciplines in the pharmaceutical industry. Quinoline was first isolated in 1834 from coal tar by F. F. Runge. Later in 1842, it was isolated as a degraded product of quinine and cinchonine.

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Quinoline (1-azanaphthalene) is one of the most versatile nitrogen-containing heterocyclic nuclei. Quinolines are a fascinating class of chemicals with varied pharmacological actions, including antitubercular,[11] antimalarial,[12] anti-convulsant,[13] antibacterial,[14] anti-inflammatory[15], anticancer,[16] including antiatherosclerotic, vasodilator, bronchodilator Klusa *et al.*, and hepatoprotective activities[17] which have drawn the interest of medicinal researchers. The eminent marketed drugs are also featured with quinoline nucleus like antibacterial-Norfloxacin, ciprofloxacin; antifungal-clioquinol; antimalarial-chloroquine, amodiaquine; antiviral activity- Elvitegravir and many more are under clinical trials.[18]

Furthermore, pyrazole another significant moiety of heterocyclic chemistry, shows a number of pharmacological activities, including antibacterial,[19] antiviral [20], anticancer,[21] antifungal,[22] antidiabetic,[23] anti-inflammatory,[24] antitubercular,[25] antimalarial.[26] A few eminent marketed drugs containing pyrazole skeleton in its chemical structure like antipyrine (antipyretic), sulphaphenazole (antibacterial), difenamizole (analgesic) and many more under clinical trials. However, it has recently been reported that the presence of pyrazole moiety with quinoline skeleton consequences in enhanced biological activity and opens up new chances for discovering lead molecules. These findings provided additional motivation for quinoline scaffold bearing pyrazole at quinoline's 3,4-b position.

Quinoline and pyrazole are significant nucleus for drug discovery and development that has gathered a lot of attention. In search of medicinal significance of quinoline bearing pyrazole hybrids as a potential therapeutic agent, it was considered worthwhile to designed and synthesized certain biologically active molecules and examine them for their antibacterial and antifungal activities *in-vitro.*

MATERIALS AND METHODS

All the derivatives of aniline and other chemicals were purchased from SD fine Chemicals Ltd. (Mumbai), CDH Pvt. Ltd. (New Delhi), reagent hydrazine hydrate from QualiChem Pvt. Ltd. (Hyderabad) and DMF from Spectrochem (Mumbai). All the equipment used were previously cleaned and sterilized before starting the processes. Melting points of all the reported analogues were examined by open capillary method using melting point apparatus (Jindal Industries, New Delhi). TLC plates were prepared using adsorbent silica gel G and homogeneity of analogues and progression of reactions was monitored with solvent system of ethyl acetate and benzene in a proportion of 9.5: 0.5. All synthesized analogues were purified through recrystallization from different solvents and characterized by spectroscopy using pellets of potassium bromide (KBr) on a fourier transform infrared spectrophotometer (FTIR-8400S) (Shimadzu, USA) and proton nuclear magnetic resonance (^{1}H-NMR) spectra of pure analogues were recorded on 400 MHz Spectrophotometer of Bruker Advance-II, Japan taken DMSO-d6 as a solvent. Stretching values of IR were reported in cm^{-1} and values of chemical shifts (δ) in parts per million.

Procedures for the Synthesis of Targeted Analogs

Step 1: General Procedure for Preparation of Acetanilide Analogs

In 5 mL acetyl chloride was introduced, followed by the addition of 5 mL glacial acetic acid (GAA) with continuous stirring. To the prepared mixture, 5 mL of various substituted anilines were added. Then the mixture was refluxed for about 20 minutes at 60°C. Allowed the mixture to cool, followed by quenching with ice-cold water and stirring vigorously. Thoroughly washed, filtered off and dried the separated solid precipitate. Recrystallization of analogs of acetanilide was performed using water and acetic acid (20:40).

Step 2: General Procedure for 2-Chloroquinoline-3-Carbaldehyde Analogues (1a-1l)

Solution of acetanilide derivatives (5 mmoles, 1.0 g) in DMF (15 mmoles, 1.72 mL), POCl3 (60 mmoles, 8.29 mL) was added drop by drop at 05°C with constant stirring and then the reaction mixture was refluxed for about 4 to 6 hours at 80 to 90°C (Vilsmeier-Haack reaction). Progression of reactions was monitored with TLC using solvents ethyl acetate and benzene. The prepared mixture was allowed to stand to make it cool, quenched into crushed ice, and stirred for approximately 5 minutes. Precipitate was filtered off with washing through distil water and dried. Recrystallization of afforded corresponding analogs of 2-chloroquinoline-3-carbaldehyde (1a-1l) was performed by ethyl acetate.

Step 3: General Procedure for Synthesis of 1H-pyrazolo[3,4-b] Quinoline Analogues (2a-2l)

Refluxing solutions of 2-chloro quinoline-3-carbaldehyde analogues (1a-1l) in solvent ethanol were treated with 1-mL of glacial acetic acid. After 10 minutes, 0.5 mL of hydrazine hydrate was added to boiling quinoline derivatives and refluxed for 5 to 6 hours for cyclization at 60°C with continuous monitoring through TLC. The resulting compound was concentrated to 10 mL on a boiling water bath. The finished product was allowed to cool before being quenched into crushed ice with continuous stirring. The solid precipitate was filtered off with thorough washing. Ethyl acetate was used for recrystallization to obtain titled compounds (Fig. 1).

Spectral Data of Synthesized Analogues (2a-2l)

1 H-pyrazolo [3, 4–b] quinoline (2a):

(Yield 64%; M.P: 313–314°C) FTIR (KBr): *v* (cm^{-1}) 3414 (stretching (stre.), N-H), 3025 (Aromatic (Ar.), stre., C-H),

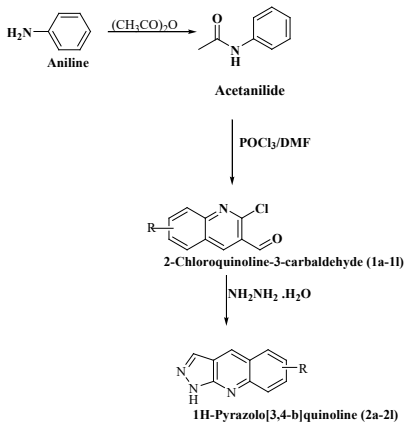

Fig. 1: Scheme for synthesis of 1H-pyrazolo [3,4-b] quinoline analogues (2a-2l) (2a R=H, 2b R= 6-Cl, 2c R= 7-Cl, 2d R=8-Cl, 2e R=7,8-Cl2, 2f R=6,7-Cl2, 2g R=6,8-Cl2, 2h R=5,7-NO2, 2i R=8-NO2, 2j R=6-NO2, 2k R=7- NO2, 2l R=6-OCH3)

1583 (Ar., stre., C = C), 1554 (stre., C =N), 1502 (stre., Ar., C=C), 1477 (Ar., stre., C -C), 1350 (stre., C -N), 762 (stre., Ar., C-Cl). ^{1}H NMR: (δ) 7.554 (pyrazole, 1 H, s), 7.623 (Ar., 1H, t), 7.671 (Ar., 1 H, t), 7.794 (Ar., 1H, d), 8.051 (Ar., 1 H, d), 8.205 (pyridine, 1H, s), 13.910 (N-H, 1H, s with D2O Exchange) ppm. (DMSO- *d6*) MS (ESI) ratio of m/z: 169.064 $[M]^+$

6-chloro-1H-pyrazolo [3, 4-b] quinoline (2b)

(Yield 63%; M.P: 330–332°C) FTIR (KBr): *v* (cm^{-1}) 3397 (stre., N- H), 3057 (Ar., stre., C-H), 1610 (Ar., stre., C=C), 1522 (Ar., stre., C = C), 1487 (stre., C = N), 1475 (stre., Ar., C -C), 1299 (stre., C -N), 770 (stre., Ar., C-Cl). ^{1}H-NMR: (δ) 7.413 (Ar., 1 H, d), 7.695 (Ar., 1H, s), 7.862 (pyrazole, 1H, s), 7.951 (pyridine, 1H, s), 8.121 (Ar., 1 H, d), 13.924 (N-H, 1H, s with D2O Exchange) ppm. (DMSO- *d6*) MS (ESI) ratio of m/z: 203.025 $[M]^+$

7-chloro-1H-pyrazolo [3,4-b] quinoline (2c)

(Yield 58%; M.P: 328–329°C) FTIR (KBr): *v* (cm^{-1}) 3429 (stre., N -H), 3072 (Ar., stre., C-H), 1595 (Ar., stre., C=C), 1515 (Ar., stre., C=C), 1495 (stre., C =N), 1467 (stre., Ar., C -C), 1325 (stre., C -N), 774 (stre., Ar., C-Cl). ^{1}H-NMR: (δ) 7.476 (Ar., H, d), 7.836 (pyrazole, H, s), 8.015 (Ar., 1 H, d), 8.305 (pyridine, 1H, s), 8.429 (Ar., 1 H, s), 13.624 (N-H, 1H, s with D2O Exchange). (DMSO- *d6*) MS (ESI) ratio of m/z: 203.25 $[M]^+$

8-chloro-1H-pyrazolo [3,4-b] quinoline (2d)

(Yield 63%; M.P: 330–331°C) FTIR (KBr): *v* (cm^{-1}) 3372 (stre., N -H), 3047 (stre., Ar., C -H), 1610 (stre., C =N), 1596 (Ar., stre., C =C), 1504 (Ar., stre., C =C), 1472 (Ar., stre., C - C), 1347 (stre., C -N), 743 (stre., Ar., C-Cl). ^{1}H-NMR: (δ) 7.433 (Ar., 1 H, t), 7.610 (pyrazole, 1H, s), 7.764 (Ar., 1 H, d), 7.933 (Ar., 1H, d), 8.125 (pyridine, 1H, s), 13.814 (N-H, 1H, s with D2O Exchange). (DMSO- *d6*) MS (ESI) ratio of m/z: 203.025 $[M]^+$

7,8-dichloro-1H-pyrazolo [3,4-b] quinoline (2e)

(Yield 62%; M.P: 329–330°C) FTIR (KBr): *v* (cm^{-1}) 3346 (stre., N-H), 3068 (Ar., stre., C-H), 1579 (Ar., stre., C = C), 1499 (Ar., stre., C =C), 1482 (stre., C =N), 1467 (stre., Ar., C -C), 1347 (stre., C -N), 761 (stre., Ar., C-Cl). ^{1}H-NMR: (δ) 7.473 (Ar., H, d), 7.602 (pyrazole, H, s), 7.681 (Ar., 1 H, d), 8.132 (pyridine, 1H, s), 13.979 (N-H, 1H, s with D2O Exchange) ppm. (DMSO- *d6*) MS (ESI) ratio of m/z: 236.986 $[M]^+$

6,7-dichloro-1H-pyrazolo [3,4-b] quinoline (2f)

(Yield 59%; M.P: 331–332°C) FTIR (KBr): *v* (cm^{-1}) 3325(stre., N -H), 3047 (Ar., stre., C -H), 1593 (Ar., stre., C =C), 1514 (stre., C =N), 1503 (Ar., stre., C =C), 1490 (stre., Ar., C -C), 1342 (stre., C -N), 743 (stre., Ar., C-Cl). ^{1}H-NMR: (δ) 7.674 (pyrazole, 1 H, s), 7.785 (Ar., 1H, s), 8.130 (Ar., 1H, s), 8.224 (pyridine, 1 H, s), 13.925 (N-H, 1H, s with D2O Exchange) ppm (DMSO- *d6*). MS (ESI) ratio of m/z: 236.986 $[M]^+$

6,8-dichloro-1H-pyrazolo [3,4-b] quinoline (2g)

(Yield 55%; M.P: 332–333°C) FTIR (KBr): *v* (cm^{-1}) 3404 (stre., N -H), 3073 (Ar., stre., C -H), 1586 (Ar., stre., C =C), 1569 (stre., C =N), 1522 (Ar., stre., C =C), 1476 (Ar., stre., C -C), 1287 (stre., C -N.), 773 (stre., Ar., C-Cl). ^{1}H-NMR: (δ) 7.711 (pyrazole, H, s), 7.834 (Ar., H, s), 7.924 (Ar., H, s), 8.212 (pyridine, 1 H, s), 13.963 (N-H, 1H, s with D2O Exchange) ppm. (DMSO- *d6*) MS (ESI) ratio of m/z: 236.986 $[M]^+$

5,7-dichloro-1H-pyrazolo [3,4-b] quinoline (2h)

(Yield 54%; M.P: 331–332°C) FTIR (KBr): *v* (cm^{-1}) 3410 (stre., N-H), 3016 (Ar., stre., C -H), 1593 (Ar., stre., C =C), 1513 (Ar., stre., C = C), 1501 (stre., C =N), 1496 (stre., Ar., C -C), 1279 (stre., C -N), 759 (stre., Ar., C -Cl). ^{1}H-NMR: (δ) 7.734 (pyrazole, 1 H, s), 7.796 (Ar., 1 H, s), 8.225 (Ar., 1 H, s), 8.734 (pyridine, 1 H, s), 14.062 (N-H, 1H, s with D2O Exchange) ppm. (DMSO- *d6*) MS (ESI) ratio of m/z: 236.986 $[M]^+$

8-nitro-1H-pyrazolo [3,4-b] quinoline (2i)

(Yield 59%; M.P:319–320°C) FTIR (KBr): *v* (cm^{-1}) 3309 (stre., N -H), 3027 (Ar., stre., C -H), 1588 (Ar., stre., C =C), 1547 (stre., N =O), 1508 (stre., Ar., C =C), 1494 (stre., C = N), 1473 (stre., Ar., C -C), 1348 (stre., C -N), 1329 (stre., N -O), 864 (stre., C -N, Nitro). ^{1}H-NMR: (δ) 7.713 (pyrazole, H, s), 7.825 (Ar., H, t), 7.942 (Ar., H, d), 8.457 (pyridine, 1H, s), 8.566 (Ar., 1 H, d), 14.113 (N-H, 1H, s with D2O Exchange) ppm.(DMSO- *d6*) MS (ESI) ratio of m/z: 214.049 $[M]^+$

6-nitro-1H-pyrazolo [3,4-b] quinoline (2j)

(Yield 56%; M.P: 318–319°C) FTIR (KBr): *v* (cm^{-1}) 3423 (stre., Ar., N -H), 3061 (Ar., stre., C-H), 1609 (Ar.., stre., C=C), 1569 (stre., N =O), 1512 (stre., C = N), 1496 (stre., A, C =C), 1465 (stre., A, C -C), 1332 (stre., N -O), 1311 (stre., C -N), 863 (stre., Nitro, C -N). ^{1}H-NMR: (δ) 7.635 (pyrazole, 1 H, s), 8.273 (Ar., 1 H, d), 8.323 (pyridine, 1 H, s), 8.482 (Ar., 1 H, d), 8.744 (Ar., 1 H, s), 14.104 (N-H, 1H, s with D2O Exchange) ppm. (DMSO- *d6*) MS (ESI) ratio of m/z: 214.049 $[M]^+$

7-nitro-1H-pyrazolo [3,4-b] quinoline (2k)

(Yield 52%; M.P: 320–321°C) FTIR (KBr): ν (cm^{-1}) 3365 (stre., N -H),3049 (Ar., stre., C -H), 1584 (Ar., stre., C =C), 1567 (stre., N = O), 1525 (stre., C =N), 1502 (Ar., stre., C =C), 1488 (Ar., stre., C - C), 1349 (stre., N -O), 1319 (stre., C -N), 861 (stre., C-N, Nitro). ^{1}H NMR: (δ) 7.613 (pyrazole, H, s), 7.933 (Ar., 1 H, d), 8.346 (Ar., 1 H, d), 8.422 (pyridine, 1H, s), 9.091 (Ar., 1 H, s), 14.205 (N-H, 1H, s with D_2O Exchange) ppm. (DMSO- d_6) MS (ESI) ratio of m/z: 214.049 $[M]^+$

6-methoxy-1H-pyrazolo-[3,4-b] quinoline (2l)

(Yield 60%; M.P.310-311°C) FTIR (KBr): ν (cm^{-1}) 3430 (stre., Ar.,N -H), 3027 (stre., Ar., C -H), 2872 (methyl, C-H), 1608 (stre., Ar., C =C), 1516 (stre., Ar., C =C), 1502 (Ar., stre., C - C), 1486 (stre., C =N), 1338 (stre., C -N), 1115 (C-O-C ether). ^{1}H-NMR: (δ) 3.685 (ether, 3 H, t), 7.621 (pyrazole, 1 H, s), 7.957 (Ar., 1 H, d), 8.242 (pyridine, 1H, s), 8.456 (Ar., 1 H, d), 9.001 (Ar., 1 H, s), 14.303 (N-H, 1H, s with D_2O Exchange) ppm. (DMSO- d_6) MS (ESI) ratio of m/z: 199.075 $[M]^+$

Evaluation of antibacterial and antifungal activities

Disc diffusion technique was performed for *in-vitro* screening of antifungal and antibacterial activities of synthesized analogs (2a-2l). Paper disc impregnated with solution of analogs in solvent DMSO at conc. of 50 μg/mL were used in this procedure. For antibacterial activity, ciprofloxacin and for antifungal activity, fluconazole were used as reference drug at a conc, of 50 μg/mL. Media of bacteria (nutrient agar media) and fungi (Sabouraud dextrose agar media) were prepared, inoculated and incubated at 37°C for 36 hours and 27°C for 72 hours, respectively. Impregnated discs were then placed over surface of media inoculated with gram-positive and gram-negative bacterial strains (*Staphyllococcus aureus, Escherichia coli*), and fungus strains (*Aspergillus niger, Candida albicans*). Inhibition zones were observed over agar media and indicate inhibition of microorganism growth. The results were interpreted in terms of the diameter of zone of inhibition (in mm) (Illustrated in Table 1).

RESULTS

As shown, main scheme demonstrates the synthesis of analogues of quinoline bearing pyrazole moiety. Characterization of resulted analogues was performed through FTIR, proton NMR and Mass spectroscopy and chemical structures of compounds was confirmed with obtained spectral data. The FTIR spectra of active resulted analogues against both bacterial and fungal strains exhibit presence of absorption bands in region 3300–3200 cm^{-1} for aromatic stretching of N-H, range of 3100–3000 cm^{-1} for stretching of aromatic C-H, 2850–2700 cm^{-1} for aldehydic C-H, 1725–1690 cm^{-1} for C=O stretching, 1600–1475 cm^{-1} for C=C and C-C stretching of aromatic rings, 1600–1450 cm^{-1} for C=N stretching, 1342–1266 cm^{-1} for C-N stretching. C-Cl Stretching was observed in the ranges of 775–700 cm^{-1}. Proton NMR spectra of analogues displayed characteristic peaks of aromatic (benzene ring) proton in the range of δ 6.5–8.5 ppm as singlet, doublet and multiplet according to the electronic environment of proton, peaks for N-H of pyrazole were observed as singlet in range of δ 13.25–14.5 ppm, peaksfor C-H of pyridine were observed as singlet in the range of δ 7.25–8.5 ppm. The ether group's C-H peak was observed in the range of δ 3.5-4.5 ppm. In mass spectra of all the targeted compounds, molecular ion peaks were all in accordance to their molecular weights. Detailed data of spectrums is mentioned in the experimental section.

Table 1: *In-vitro* antibacterial and antifungal activity of synthesized analogues (Diameter of zone of inhibition in mm)

Compound code	*Staphylococcus aureus*	*Escherichia coli*	*Aspergillus niger*	*Candida albicans*
2a	9.57 ± 0.22	14.36 ± 0.42	9.7 ± 0.5	15.2 ± 0.56
2b	14.6 ± 0.36	16.28 ± 0.35	11.6 ± 0.36	13.62 ± 0.78
2c	17.48 ± 0.62	20.49 ± 0.23	19.31 ± 0.2	22.49 ± 0.23
2d	13.21 ± 0.64	17.11 ± 0.80	13.37 ± 0.45	15.77 ± 0.5
2e	18.16 ± 0.17	22.09 ± 0.82	17.7 ± 0.42	19.42 ± 0.7
2f	9.05 ± 0.42	12.58 ± 0.91	12.45 ± 0.24	15.9 ± 0.12
2g	14.06 ± 0.69	17.37 ± 0.76	16.64 ± 0.96	18.54 ± 0.5
2h	19.04 ± 0.81	21.37 ± 0.23	23.15 ± 0.7	21.11 ± 0.36
2i	14.14 ± 0.56	17.6 ± 0.48	14.85 ± 0.65	13.4 ± 0.73
2j	12.1 ± 0.41	15.55 ± 0.54	10.81 ± 0.61	13.39 ± 0.14
2k	20.45 ± 0.15	19.57 ± 0.25	20.6 ± 0.34	19.62 ± 0.4
2l	19.86 ± 0.28	20.16 ± 0.43	21.23 ± 0.44	22.25 ± 0.32
Ciprofloxacin	22.5 ± 0.25mm	23.6 ± 0.4mm	-	-
Fluconazole	-	-	24.4 ± 0.5mm	23.5 ± 0.25 mm

DISCUSSION

Twelve analogues of quinoline-bearing pyrazole moiety were prepared and examined for antimicrobial activities. Culture media for bacterial growth was prepared through soybean casein digest media (SCDM) while for fungal growth Sabouraud dextrose agar media was used. Spectroscopy analysis was used to elucidate the chemical structures of synthesized compounds. Table 1 concludes that, resulted compound 2e exhibits promising antibacterial activity with inhibition zone of 22.09 ± 0.82 mm specific to *E. coli* and 2k exhibited promising activity against *S. aureus* with inhibition zone of 20.45 ± 0.15 mm(at conc. 50 µg/mL) compared to reference drug ciprofloxacin at same concentration. Analogue 2 hours exhibited promising antifungal activity against *A. niger* with inhibition zone of 23.56 ± 0.7 mm. Analogues 2c and 2l exhibited equal potency against *C. albicans* with inhibition zone of 22.49 ± 0.23 and 22.25 ± 0.32 mm, respectively (conc. 50 µg/mL) in comparison to standard drug fluconazole. These newly compounds can be further exploited to get potent lead molecules.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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