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1,3,4-Thiadiazole: A Promising Pharmacophore

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ABSTRACT

Active pharmaceutical ingredients (A.P.I.) are made up of various heteroatomic moieties. Numerous heterocycle scaffolds are regarded as crucial structures. More frequently, presence of various heteroatoms viz. nitrogen, sulphur, halogens, and oxygen atoms at different position in 5- or 6-membered rings contributed them as valued source of therapeutic profiles in literature of medicinal chemistry. In the current study, numerous novels 1,3,4-thiadiazole derivatives were created using a multi-step synthetic method. These thiadiazole derivatives comprised 2-amino-5-phenyl-1, 3,4-thiadiazole, piperazine, acetophenones, and quinolin-5-ol. ^{1}H-NMR, IR, Mass and elemental analyses were used to describe these thiadiazole derivatives (C,H,N). The antibacterial, antifungal, and insecticidal efficacy of thiadiazole 4a-4i mimics was investigated.

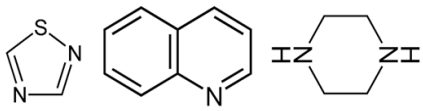
Keywords: 1,3,4-thiadiazoles, Antibacterial, Antifungal and Insecticidal.

INTRODUCTION

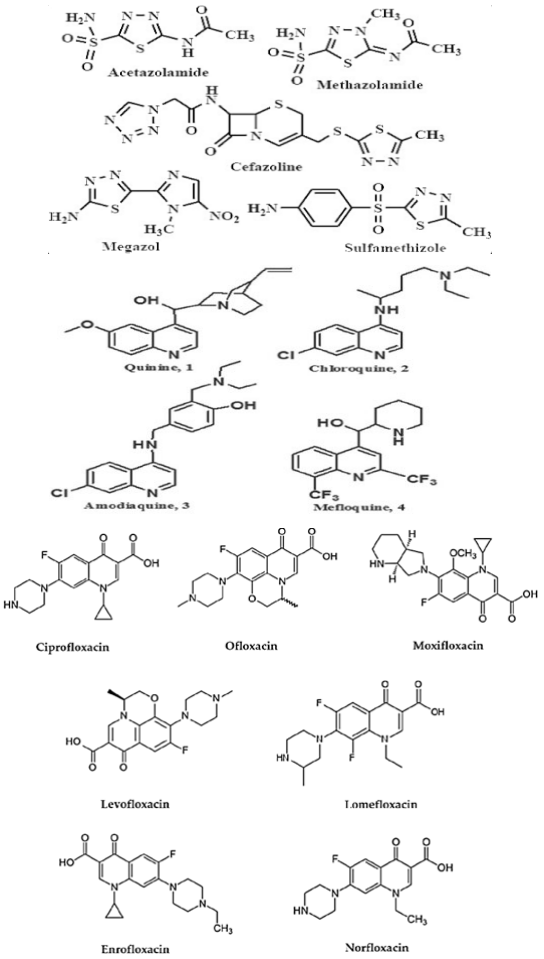
Fitness and ailment are the aspects of the lifestyles. Wholesome peoples can serve higher for the society and the clinical community is successfully maintaining their fitness issues. It is medicinal chemistry that powers this scientific strategy. Chemotherapeutic potential of different heteroatom moieties, viz. triazoles, azetidinones, thiazolidinones, thiadiazoles, coumarins, quinolines, indoles and many others; enlightened by medicinal chemistry. It is estimated that more than 85% of all FDA-approved drugs in the market are simply heterocyclic molecules. It is believed that within the approaching decade, an extra phase of novel heteroatoms-based current drug designed synthesis is to come back. There has been a rapid growth marked in studies of heterocyclic moieties as a result of emerging synthetic methodologies such as highly electron-donating, strong coordination abilities, metal-catalyzed cross-coupling and hetero-coupling reactions, that facilitates medicinal research workers for the speedy development of a vast range of bioactive heterocyclic derivatives.

Nonetheless, antimicrobial resistance (AMR) has been identified by the WHO as the greatest health hazard to the world today. The

improper and excessive use of antimicrobial agents is a key contributor to the development of antibiotic resistance. We need a world-wide push from the scientific community to achieve sustainable improvement dreams (SDGs). It is found that several heterocyclics considered as privilege structural units. Frequent literature survey evidenced the various pharmacology of diverse nitrogen, sulphur, bearing heteroatomic mimics. Furthermore, substituted heterocyclic moieties bearing thiadiazole[1-9], quinoline[10-17] and piperazine[18-24] demonstrated great biological profiles.



We have preferred quinoline and thiadiazole as our two building blocks in the context of literature analysis. Information explored the approaches of thiadiazole ring as many therapeutic agents are in marketplace with unique names like acetazolamide used as carbonic anhydrase inhibitors, methazol amide as diuretic medicines, cefazolin (1st generation of cephalosporin) sulfonamide, sulfamethizole both as antimicrobial drugs while megazol as antiparasitic agent. At the same time, quinoline bearing derivatives are also properly famed as existing drug in market for their versatile scientific uses like quinine, chloroquinine, amodiaquine, mefloquine for malaria, carteolol for high blood pressure, angina, ciprofloxacin, ofloxacin, moxifloxacin, levofloxacin, lomefloxacin, enrofloxacin, norfloxacin for bacterial remedy. By reviewing these encouraging pharmacological properties, we continue our work on the design, synthesis, and organic assessment of several targeted substituted thiadiazole congeners in order to attain our novel heterocyclic moiety development programme[25–30]. Based on our research, we chose two building blocks: quinoline and thiadiazole. Data examined the use of the thiadiazole ring because there are numerous medicinal drugs available on the market under various names, such as acetazolamide, which are utilised as carbonic anhydrase inhibitors, methazol amide as diuretic medicines, cefazolin (1st generation cephalosporin) sulfonamide, sulfamethizole both as antimicrobial agents while megazol as antiparasitic drug. While on the other side, quinoline bearing derivatives are also well famed as drug market for their versatile clinical uses viz. quinine, chloroquinine, amodiaquine, mefloquine for malaria, carteolol for hypertension, angina, ciprofloxacin, ofloxacin, moxifloxacin, levofloxacin, lomefloxacin, enrofloxacin, norfloxacin for bacterial treatment.



By developing, synthesizing, and biologically evaluating a number of targeted substituted thiadiazole congeners, we move on with our development programme of novel heterocyclic moieties[25–30] in light of the aforementioned research of these promising pharmacological characteristics.

RESULTS & DISCUSSION

1-(*p*-tolyl)-1H-[1,3]oxazino[5,6-*f*]quinolin-3-one 1 was prepared by refluxing of acetophenone, carbamide with quinolin-5-ol in ethanol. By using phosphorous oxychloride to chlorinate derivative 1 was chlorinated to yield 3-chloro-1-(*p*-tolyl)-1*H*-[1,3] oxazino[5,6-*f*] quinoline 2. Derivative (1-(*p*-tolyl)-

1*H*-[1,3] oxazino[5,6-*f*]quinolino)-4-piperazine i.e., 3 obtained by the condensation reaction between derivative 2 and piperazine. Refluxing of derivative 3 and 5-phenyl-2-amino-1,3,4-thiadiazoles[31] furnished the target mimics [2-*p*henyl-1-(*p*-tolyl) pyrido[3,2-*f*]quinazolin-4(1*H*)-yl]-1,3,4-thiadiazolyl)]-4-piperazine 4a-4i. A total of six microbial strains were designated for *In vitro* antimicrobial activity of target congeners 4a-4i. Among the three bacteria, one was *Gram-positive Staphylococcus aureus* while 2 others were *Gram-negative*; *Proteus vulgaris* and *Escherichia coli*. Antifungal testing was performed on *Aspergillus fumigatus* (plant isolate), *Candida krusei* G03 and *Candida albicans* ATCC 2091. Furthermore, thiadaizole scaffolds were also tested for insecticidal screening in groups of cockroaches (*Periplaneta americana*).

MATERIALS AND METHODS

Materials

S D Fine Chem Limited (SDFCL), Qualigen Fine Chemicals and E. Merck Ltd., selected for raw materials for the preparation. Fluconazole and ampicillin trihydate antimicrobials were obtained from Ind-Swift Pharmaceuticals and parathion from Joshi Agrochem Pharma Pvt. Ltd. Derivatives were tested for their physical characterization. TLC performed over the silica gel coated glass plates to know the endpoint of the synthesis. Spots visualization was performed in iodine chamber. Heraeus CHN fast analyzer was used to conduct elemental analysis of all derivatives, and Results were found to be within 0.4 percent of their theoretical counterparts. For infrared spectroscopy, the KBr pellets used with FTIR spectrometer (Perkin Elmer system 2000) while Bruker DPX 200 for ^{1}H-NMR spectroscopy.

Antimicrobial activity

Filter paper disc diffusion methodology[32-33] adopted for performed *In vitro* antimicrobial activity. Inhibition zone's diameter was calculated in mm. Nutrient agar has been utilized as culture medium. Culture medium was developed by using sabourad dextrose agar. A concentration of 250 g/mL in 10% DMSO and prepared compounds. Ampicillin trihydrate and fluconazole employed as standards for both the activity.

Insecticidal activity

Microlitre syringe method[34] was adopted for the insecticidal activity. Groups maintained and each group contained six cockroaches. 4th along with 5th abdominal segments of ventral side of insect was selected to insert acetonic solution of standard parathion (0.02 mL of 5 g/L) and different test compounds by microliter syringe. Acetone used as control. During insecticidal activity, no food was given and the time taken until 100% mortality was recorded. Student's t-test was used to assess both the standard and calculated data for statistical significance.

EXPERIMENTAL

Synthesis of 1-(*p*-tolyl)-1*H*-[1,3]oxazino[5,6-*f*] quinolin-3-one (1)

Quinolin-5-ol, carbamide and acetophenone have been mixed in ethanol during stirring for 10 min at room temperature before refluxing for 1.5 hours. On completion, the reaction mixture has been cooled by being put into ice-water while being stirred, filtered, and then recrystallized using methanol: R_f: 0.69, m.p: 171^{0}C; Yield: 67%. "IR (cm^{-1}): 1279 (-C-O-C-), 1588 (-C=N-), 1620 (-C…C- aromatic ring), 1742 (C=O), 3420 (NH). ^{1}H-NMR ($CDCl_3$, δ): 2.33 (s, 3H, -CH_3), 4.70 (s, 1H, CH-NH), 6.75 (bs, 1H, -NH-), 7.40-8.66 (m, 9H, H-Ar). Anal. calcd. for $C_{18}H_{14}N_2O_2$: N, 9.65; H, 4.86; C, 74.47; found N, 9.57; H, 4.88; C, 74.66. MS (m/z, %) 290.11."

Synthesis of 3-chloro-1-(*p*-tolyl)-1*H*-[1,3] oxazino[5,6-*f*] quinoline (2)

Compound 1 was dissolved in toluene and heated to a reflux for 1.5 h before phosphorous oxychloride (0.015mol) was added drop by drop. Extra toluene was removed using distillation. After being put into cold water and stirred, the reaction mixture was neutralised with 3 percent KOH solution, recrystallized, and filtered in ethanol: "R_f: 0.72, m.p: 133^{0}C, Yield: 62%, IR (cm^{-1}): 1620 (-C…C- aromatic ring), 1285 (-C-O-C-), 1580 (-C=N-). ^{1}H-NMR ($CDCl_3$, δ): 2.89 (s, 3H, -CH_3), 4.88 (s, 1H, CH-N-C), 7-38-8.56 (m, 9H, Ar-H). Anal. calcd. for $C_{18}H_{13}ClN_2O$: N, 9.07; H, 4.24; C, 70.02; found N, 9.12; H, 4.17, C, 70.14. MS (m/z, %) 308.07".

Synthesis of (1-(*p*-tolyl)-1*H*-[1,3]oxazino[5,6-*f*] quinolino)-4-piperazine (3)

Compound 2 and piperazine anhydrate mixed in a methanolic solution for 15 min at 40°C before refluxing for 2.5 hours. The methanol solvent

was distilled until there was no excess, and then chilled ice water poured to the residue, washed, and filtered. Crude was recrystallized in aqueous ethanol: R_f: 0.67; m.p.: 156^{0}C; Yield: 70%. IR (KBr, cm^{-1}): 1616 (C…C of aromatic ring), 1273 (C-O-C), 1571 (C=N). ^{1}H-NMR ($CDCl_3$, δ/ppm): 1.70-2.66 (m, 9H, piperazine), 2.80 (s, 3H, -CH_3), 4.78 (s, 1H, CH-N-C), 7.27-8.44 (m, 9H, Ar-H), Anal. calcd. for $C_{22}H_{22}N_4O$: N, 15.63; H, 6.19; C, 73.72; found N, 15.47; H, 6.11; C, 73.68. MS (m/z, %) 358.18.

Synthesis of [2-*p*henyl-1-(*p*-tolyl)pyrido[3,2-*f*] quinazolin-4(1*H*)-yl]-1,3,4-thiadiazolyl)] -4-piperazine (4a-4i)

Derivative 3 (0.002 mol) and 2-amino-5-phenyl-1,3,4-thiadiazole (0.002 mol) were refluxed in isopropanol for 2-3 hours. Distillation has been used to retrieve solvent once the process of preparation was finished. The necessary compounds 4a-4i were obtained by dumping the residue into broken ice, washing it with petroleum ether (40-60°C), and then recrystallizing it in the suitable solvents.

Compound 4a: R_f: 0.66; m.p.: 231^{0}C; Yield: 58%. "IR (cm^{-1}): 1625 (-C…C- aromatic ring), 681 (C-S-C), 1289 (-C-O-C-), 1360 (-N-N-), 1598 (-C=N). ^{1}H-NMR ($CDCl_3$, δ): 1.58-2.60 (m, 9H, piperazine), 2.95 (s, 3H, -CH_3), 4.65 (s, 1H, -CH-N-C-), 7.51-8.75 (m, 14H, H-Ar), Anal. calcd. for $C_{30}H_{27}N_7S$: N,18.94; H, 5.26; C,69.61; found N,19.18; H,5.20; C,69.55. MS (m/z, %) 517.20.

Compound 4b: R_f: 0.70; m.p.: 111^{0}C; Yield: 43%. IR (cm^{-1}): 1615 (-C…C- aromatic ring), 673 (-C-S-C-), 1281 (-C-O-C-), 1366 (-N-N-), 1577 (-C=N-). ^{1}H-NMR ($CDCl_3$, δ): 1.63-2.50 (m, 9H, piperazine), 3.05 (s, 3H, -CH_3), 4.79 (s, 1H, -CH-N-C-), 7.55-8.70 (m, 13H, H-Ar). Anal. calcd. for $C_{30}H_{26}N_7ClS$: N,17.76; H,4.75; C,65.26; found N,17.85; H,4.70; C,65.40. MS (m/z, %) 551.17.

Compound 4c: Yield: 51%; R_f: 0.64; m.p.: 130^{0}C. IR (cm^{-1}): 1620 (-C…C- aromatic ring), 670 (-C-S-C-), 1272 (-C-O-C-), 1351 (-N-N-), 1590 (-C=N-). ^{1}H-NMR ($CDCl_3$, δ): 1.60-2.62 (m, 9H, piperazine), 3.00 (s, 3H, -CH_3), 4.56 (s, 1H, -CH-N-), 7.33-8.72 (m, 13H, H-Ar), Anal. calcd. for $C_{30}H_{26}N_7ClS$: N,17.76; H,4.75; C,65.26; found N,17.65; H,4.61; C,65.18. MS (m/z, %) 551.17.

Compound 4d: R_f: 0.56; m.p.: 106^{0}C; Yield: 52%. IR (cm^{-1}): 1618 (-C…C- aromatic ring), 692 (-C-S-C-), 1282 (-C-O-C-), 1358 (-N-N-), 1584 (-C=N-). ^{1}H-NMR ($CDCl_3$, δ): 1.45-2.56 (m, 9H, piperazine), 3.10 (s, 3H, -CH_3), 4.48 (s, 1H, -CH-N-), 7.40-8.68 (m, 13H, H-Ar). Anal. calcd. for $C_{30}H_{26}N_7ClS$: N,17.76; H,4.75; C,65.26; found N,17.86; H,4.70; C,65.22. MS (m/z, %) 551.17.

Compound 4e: Rf: 0.62; m.p.: 154^{0}C; Yield: 62%. IR (cm^{-1}): 1650 (-C…C- aromatic ring), 688 (-C-S-C-), 1280 (-C-O-C-), 1360 (-N-N-), 1590 (-C=N-). ^{1}H-NMR ($CDCl_3$, δ): 1.50-2.50 (m, 9H, piperazine), 2.94 (s, 3H, -CH_3), 4.60 (s, 1H,-CH-N-), 7.47-8.70 (m, 13H, H-Ar). Anal. calcd. for $C_{30}H_{26}N_8O_2S$: N,19.92; H,4.66; C,64.04; found N, 20.07; H,4.59; C, 64.23. MS (m/z, %) 548.17.

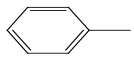
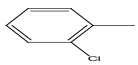
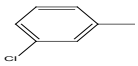
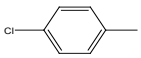
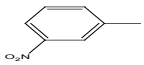
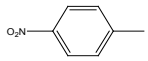
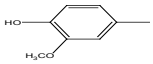
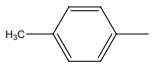
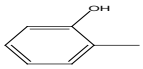
Compound 4f: Rf: 0.65; m.p.: 138^{0}C; Yield: 57%. IR (cm^{-1}): 1641 (-C…C- aromatic ring), 681 (-C-S-C-), 1267 (-C-O-C-), 1343 (-N-N-), 1600 (-C=N-). ^{1}H-NMR ($CDCl_3$, δ): 1.48-2.61 (m, 9H, piperazine), 3.05 (s, 3H, -CH_3), 4.55 (s, 1H, -CH-N-), 7.33-8.61 (m, 13H, H-Ar). Anal. calcd. for $C_{30}H_{26}N_8O_2S$: N,19.92; H,4.66; C,64.04; found N,19.89; H,4.70; C,64.12. MS (m/z, %) 548.17.

Compound 4g: R_f:0.68; m.p.: 201^{0}C; Yield: 65%. IR (cm^{-1}): 1637 (-C…C- aromatic ring), 681 (-C-S-C-), 1289 (-C-O-C-), 1360 (-N-N-), 1563 (-C=N-). ^{1}H-NMR ($CDCl_3$, δ): 1.51-2.59 (m, 9H, piperazine), 3.02 (s, 3H, -CH_3), 3.63 (s, 3H, -OCH_3), 4.66 (s, 1H, -CH-N-), 7.39-8.61 (m, 12H, H-Ar), 12.50 (bs, 1H, HO-Ph). Anal. calcd. for $C_{31}H_{29}N_7SO_2$: N,17.39; H,5.19; C,65.05; found N,17.55; H,5.31; C,64.93. MS (m/z, %) 563.21.

Compound 4h: R_f: 0.70, m.p.: 173^{0}C; Yield: 58%. IR (cm^{-1}): 1656 (-C…C- aromatic ring), 1565 (-C=N-), 1367 (-N-N-), 1249 (-C-O-C-), 682 (-C-S-C-). ^{1}H-NMR ($CDCl_3$, δ): 1.02 (s, 3H, -CH_3), 1.58-2.45 (m, 9H, piperazine), 3.11 (s, 3H, -CH_3), 4.90 (s, 1H, -CH-N-), 7.34-8.55 (m, 13H, H-Ar). Anal. calcd. for $C_{31}H_{29}N_7S$: N,18.44; H,5.50; C,70.03; found N,18.50; H,5.41; C,69.87. MS (m/z, %) 531.22.

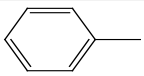
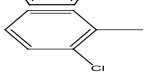
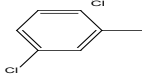
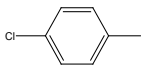
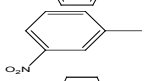
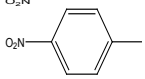
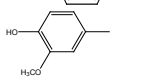
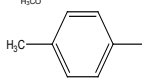
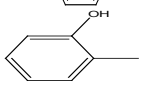
Compound 4i: R_f: 0.64; m.p.:125^{0}C; Yield: 51%. IR (cm^{-1}): 1625 (-C…C- aromatic ring), 681 (-C-S-C-), 1289 (-C-O-C-), 1360 (-N-N-), 1598 (-C=N). ^{1}H-NMR ($CDCl_3$, δ): 1.58-2.45 (m, 9H, piperazine), 3.11 (s, 3H, -CH_3), 4.51 (s, 1H, -CH-N), 7.35-8.61 (m, 13H, H-Ar), 12.35 (bs, 1H, HO-Ph). Anal. calcd. for" $C_{30}H_{27}N_7SO$: N,18.37; H,5.10; C,67.52; found N,18.26; H,4.98; C,67.67. MS (m/z, %) 533.20.

Table 1: Antibacterial and antifungal screening of [2-*p*henyl-1-(*p*-tolyl)*p*yrido[3,2-*f*]quinazolin-4(1*H*)-yl]-1,3,4-thiadiazolyl)]-4-piperazine (4a-4i)

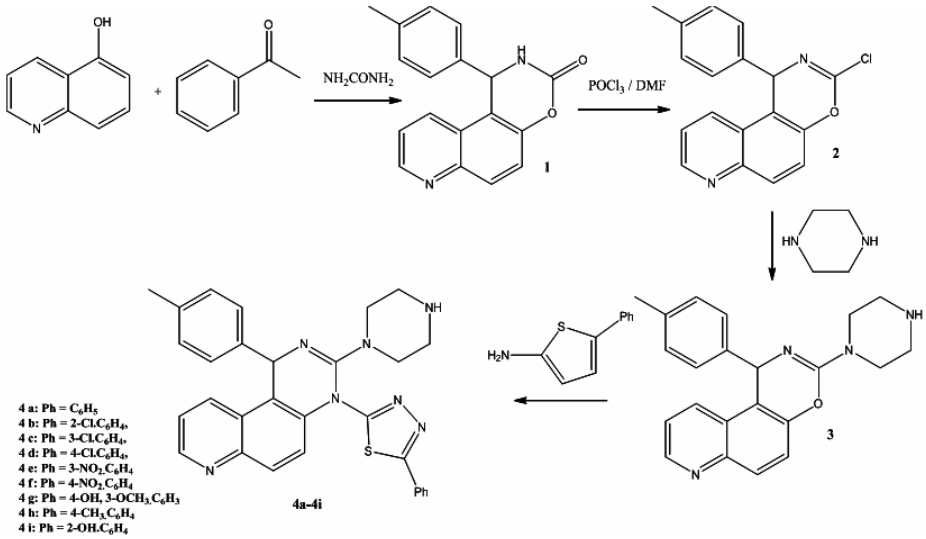
Compound	Ph	Antibacterial activity			Antifungal activity		
		S. aureus	*E. coli*	*P. vulgaris*	*A. fumigatus*	*C. albicans ATCC 2091*	*C. krusei G03*
4a		6	0	6	6	0	0
4b		14	16	14	6	16	16
4c		12	16	12	10	12	14
4d		14	18	14	12	16	18
4e		10	8	8	10	12	12
4f		8	10	12	0	10	10
4g		10	12	10	0	10	8
4h		10	12	12	6	6	8
4i		12	14	14	8	12	16
Ampicillin trihydrate		16	20	20	-	-	-
Fluconazole		-	-	-	0	29	20

Concentration = 250g/mL in 10% DMSO, (-) means no activity performed, (0) displayed no inhibition

Table 2: Insecticidal activity of [2-*p*henyl-1-(*p*-tolyl)pyrido[3,2-*f*] quinazolin-4(1*H*)-yl]-1,3,4-thiadiazolyl)]-4-piperazine (4a-4i)

Compound	Ph	Concentration	Mean killing time (min)
4a		5 g/L	470.5+15.10***
4b		5 g/L	270+4.85**
4c		5 g/L	260.2+4.10*
4d		5 g/L	368+7.20***
4e		5 g/L	432.6+10.31***
4f		5 g/L	330.4+5.33**
4g		5 g/L	388+6.55**
4h		5 g/L	302+5.80**
4i		5 g/L	500+9.75***
		10 g/L	220+8.00***
		20 g/L	200+7.17***
Parathion		5 g/L	282+11.76$^{\Delta\Delta\Delta}$
		10 g/L	248+9.30$^{\Delta\Delta\Delta}$
		20 g/L	230+14.70$^{\Delta\Delta\Delta}$

@acetone, n=6 cockroaches in each group; P<0.05, P<0.01, P<0.001 in comparison to control; ¥P<0.05, ¥¥P<0.01, ¥¥¥P<0.001



Scheme 1

CONCLUSION

Insecticidal and antimicrobial activity of compounds 4a-4i evidenced promising biological utility of pharmacophores; thiadiazole, quinoline and piperazine. Clinical results explored that compounds 4b, 4c, 4d and 4i substituted with 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl and 2-hydroxyphenyl respectively showed better pharmacological evaluation. These derivatives possessed statistically good antibacterial and antifungal activity but less than standards used (Table 1). Analysis of insecticidal activity cleared that these compounds also displayed prominent insecticidal activity (Table 2) in comparison to the parathion at all concentrations used. Various substitution performed well over the block structure thiadiazoles and displayed appropriate orientation to the potential receptor site. Structure activity relationship (S.A.R.) of the compounds 4a-4i revealed that conversion of derivative 3 into different substituted 1,3,4-thiadiazoles 4a-4i via condensation with 2-amino-5-phenyl-1,3,4-thiadiazole improved biological activities. Furthermore S.A.R. revealed that halogen substituted thiadiazoles caused better antimicrobial inhibition. But among these, 2-chlorophenyl substitution found beneficial towards antimicrobial activity while on the other hand 2-hydroxyphenyl substitution caused significant insecticidal potential. Above study cleared the biological potential of quinoline, thiadiazole and piperazine which impelled to explore more in the same stream.

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Conflict of interest

The author declare that we have no conflict of interest.

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