Plant Archives Vol. 21, No. 2, 2021 pp. 675-681 e-ISSN:2581-6063 (online), ISSN:0972-5210

Plant Archives

Journal homepage: http://www.plantarchives.org
DOI Url : https://doi.org/10.51470/PLANTARCHIVES.2021.v21.no2.104

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 2-(4-BROMOBENZYLIDIN) AMINO-5-METHYL-*N*-PHENYL-7-SUBSTITUTED PHENYL-4,7-DIHYDRO(1,2,4)TRIAZOLO (1,5-a)-6-CARBOXAMIDOPYRIMIDINES

Nidhi Chaudhary[1], Ranjana Dubey[2], Tilak Ram[3] , Pradeep Kumar[4] and Hament Panwar[4*]
[1]Department of Chemistry, M.I.E.T., Meerut-250001, U.P., India
[2]Department of Chemistry, S.R.M. University, Modinagar-201204, Ghaziabad, U.P., India
[3]Department of Chemistry, Government P.G. College, Uttarkashi-249193, U.K., India
[4*]Department of Chemistry, H.V.M. (P.G.) College, Raisi, Haridwar-247671, U.K., India
[*]Corresponding author: E-mail Id: drhp.hvm@gmail.com

(Date of Receiving : 01-05-2021; Date of Acceptance : 24-08-2021)

ABSTRACT

Several substituted carboxamido pyrimidine derivatives (3a-g) were synthesized by conventional methodology. Structure of different substituted pyrimidines characterized by IR, ^{1}H-NMR, Mass and elemental analysis (C, H, N). Furthermore, these substituted pyrimidines were screened for their different biologically activity viz. antibacterial, antifungal, insecticidal and anthelmintic activities. Some substituted pyrimidines displayed significant biological potential under applied pharmacological conditions.

Keywords : 1,2,4-Triazoles, pyrimidines, schiff bases, antibacterial, antifungal, insecticidal, anthelmintic activity.

INTRODUCTION

Among the various problems of society, two major problems have a common approach to every community of every place. These two problems are health and food under the circumstances of covid 19. These two are directly proportional to each other as good food nourish the body well. But drug resistance and food will be a big challenge in coming days. By 2050, rate of population growth is expected to be raised up to 10 billion then food production rate will also face new challenges to meet this challenge (Ganie *et al*., 2020; Hickey *et al*., 2019; FAO, 2020). Problems of microbes, weed (FAO, 2020; Adetunji *et al*., 2019), insect, will be severe and it results in higher consumption of antimicrobials, herbicides and insecticides. More uses of chemicals viz. antimicrobials, pesticides, insecticides and herbicides influenced drug resistance (Pannell *et al*., 2017; IACG, 2019; Varadraj *et al*., 2018), lower nutrition value of crops, contamination (Pussemier *et al.,* 2006; Baker *et al*., 2002), poor production of crops (Brun *et al*., 2020), direct or indirect loss of fertility of soils and at last not least it results into higher crop cultivation cost (Bahadur *et al*., 2015). Among the all-life threatening issues antimicrobial drug resistance is the big life health issue (AMR, 2021). Recurrent designing of novel synthetic drug is the only way to overcome of it (Kumar *et al*., 2003; Panwar *et al*., 2006; Panwar *et al*., 2011; Panwar *et al*., 2011; Panwar *et al*., 2012; Panwar *et al*., 2013). Substituted triazoles recognised for their antimycobacterial (Ashok *et al*., 2018; Pogaku *et al*., 2019), antiproliferative (Pogaku *et al*., 2019), antitubercular (Phatak *et al*., 2019; Shaikh *et al*., 2015), antimicrobial (Ashok *et al*., 2018; Strzelecka and Swiatek, 2021; Demirbas *et al*., 2009; Bayrak *et al.,* 2009), anti-inflammatory (Li *et al*., 2020), analgesic (Khanage *et al*., 2013), antidiabetic (Hichri *et al*., 2019), anticonvulsant (Kapron *et al*., 2020). Since last few decades several pyrimidine derivatives were reported to have wide clinical and pharmacological applications viz. antibacterial (Kompis and Wick, 1977; Sharma *et al*., 2004; Roth and Chegg, 1982), antifolates (Werkheiser, 1961), antiviral (Balzarini and McGuigan, 2002), anticancer (Coe *et al*., 1996), antidaibetic (Lee *et al*., 2005). Above literature review impelled us to design some novel heterocyclics by combining triazoles, pyrimidines and furthermore they were pharmacological evaluated for their antibacterial, antifungal, insecticidal, anthelmintic activities.

MATERIALS AND METHODS

Experimental

Melting points of synthesised target derivatives 3a-g determined in open glass capillaries by using thermonic melting points apparatus and are uncorrected. Silica gel G coated plates were used to analyse homogeneity of the newly prepared pyrimidines and spots were located by using iodine chamber. C, H, N elements were detected by Heraeus CHN rapid analyser. Results ranged within the ± 0.4 % of theoretical values. Infrared spectral analysis done by Perkin

Elmer system 2000 FTIR spectrometer while ^{1}H NMR spectra on Bruker DPX 200 using TMS as internal standard.

PHARMACOLOGICAL EVALUATION

Antimicrobial evaluation

Substituted 6-carboxamidopyrimidines (3a-g) were tested for preliminary antibacterial and antifungal activity by disk diffusion method (Cruickshank *et al.*, 1975, Collins, A. H., 1976) against the particular strains of bacteria and fungi. During screening used bacterial and fungal strains were *Staphylococcus aureus, Escherichia coli*, *Klebsiella pneumoniae* and *Aspergillus fumigatus* (plant isolate), *Candida crusei* and *Candida glabrata* respectively. Whatmann no.1 filter paper was used in making of disks of size of 6.25 mm in diameter by punching. Batches of 100 disks were dispensed to each screw-capped bottle which was sterilized by dry heating at 140 °C for an hour. Solutions of 6-carboxamidopyrimidines were prepared in DMF solvent. The incubation performed at 37 °C for 24 h. Standard drugs ampicillin trihydrate and fluconazole were used in preliminary antimicrobial testing. During antimicrobial testing solvent and growth controls were kept and zones of inhibition were noted in mm. The bacterial as well as fungal inhibitory zones (mm) of targeted substituted 6-carboxamidopyrimidines recorded in Table 1. During antifungal activity sabouraud's agar media prepared by liquefying peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and pH was adjusted to 5.7. Normal saline was used to make a suspension of the spore of fungal strain for lawing. Selected fungal strains transferred to 3 ml saline to get a suspension of the corresponding species. Agar media (20 ml) was poured into each petri dish. Excess suspension was decanted and the plates were dried in the incubator at 37 °C for 1 h. Agar punch well were made and labelled also. A control was also prepared in triplicate and maintained at 37 °C for 3–4 days.

Insecticidal study

Insecticidal activity of substituted 6-carboxamidopyrimidines was performed on *Periplaneta americana.* Two doses were selected for insecticidal activity i.e., 1% and 2% in acetone. Acetone solutions of the substituted 6-carboxamidopyrimidines (2a-g & 3a-g) were injected in between 4th and 5th abdominal segment on the ventral side of the body of *P. americana* with the help of micro syringe. Death time of cockroaches was recorded as knock down (KD) value. All insecticidal activity was equaled with standard cypermethrin drug used. Death time was considered when the antennae of *P. americana* were motionless, the appendages shrunken and folded towards the ventral side and cockroach lay dorsally (Chaudhary *et al*., 2014) (Table-2).

Anthelmintic activity

Indian adult earthworms (*Pheretima posthuma*) were used for the anthelmintic activity which were collected from moist soil, washed with normal saline to remove all stacked faecal matter over the surfaces. Prepared substituted pyrimidine derivatives 2a-g & 3a-gwere dissolved in the least amount of DMF and the volume adjusted to 10 ml with saline water. All the solutions of synthesized pyrimidines and drugs solutions were freshly prepared. Albendazole was used as reference drug. Different groups of six earthworms released into desired formulations after the paralytic and lethal time noted. Paralysis and death time of individual earthworm was noted. In activity death was concluded by losing their motility followed by fading away of their body colour (Nirmal *et al*., 2007; Tambe *et al.*, 2006; Vilgar, 1984) (Table-3).

ORGANIC SYNTHESIS

General method of preparation of 2-amino-5-methyl-*N*,7-diphenyl-4,7-dihydro (1,2,4) triazolo (1,5-a)-6-carboxamidopyrimidines (2a-g)

A mixture of compound 1 (Gamma *et al.*, 2015) i.e., 3-oxo-N-phenylbutanamide, 4*H*-1,2,4-triazole-3,5-diamine (0.01 mol) and different substituted aromatic aldehydes (0.01 mol) were taken in N, N-DMF and stirred for 30 minutes. A few drops of conc. hydrochloric acid added to the reaction mixture and allowed to stir at RT for 1 hr. followed by refluxing for 4-6 hrs. Progress of reaction routinely checked by TLC. On completion of reaction excess of solvent distilled away. Cooled residue poured in ice water, filtered and triturated with petroleum ether (40-60 ^{o}C). Different prepared substituted pyrimidines were recrystallized by appropriate solvents.

2a: IR (KBr, $\nu_{max,}$ cm^{-1}): 3400 (N-H), 3110 (C…C of aromatic ring), 1695 (C=O), 1588 (C=N), 1468 (N-N), 1251 (C-N). ^{1}H NMR ($CDCl_3$, δ ppm): 10.15 (s, 1H, Ph-NH-CO-), 7.88-7.15 (m, 10H, ArH), 6.50 (s, 2H, -NH_2), 5.07 (s, 1H, CH-Ph), 3.94 (s, 1H, NH), 1.88 (s, 3H, -CH_3). MS: $(M)^+$ 346.15 at m/z. Anal. calcd. (%) for $C_{19}H_{18}N_6O$: C, 65.88; H, 5.24; N, 24.26; found (%): C, 65.90; H, 5.20; N, 24.33.

2b: IR (KBr, $\nu_{max,}$ cm^{-1}): 3410 (N-H), 3105 (C…C of aromatic ring), 1690 (C=O), 1585 (C=N), 1460 (N-N), 1256 (C-N), 668 (C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 10.04 (s, 1H, Ph-NH-CO-), 7.80-7.22 (m, 9H, ArH), 6.44 (s, 2H, -NH_2), 5.02 (s, 1H, CH-Ph), 3.90 (s, 1H, NH), 1.80 (s, 3H, -CH_3). MS: $(M)^+$ 380.12 at m/z. Anal. calcd. (%) for $C_{19}H_{17}ClN_6O$: C, 59.92; H, 4.50; N, 22.07; found (%): C, 60.11; H, 4.39; N, 22.30.

2c: IR (KBr, $\nu_{max,}$ cm^{-1}): 3406 (N-H), 3109 (C…C of aromatic ring), 1682 (C=O), 1580 (C=N), 1466 (N-N), 1255 (C-N), 671 (C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 10.10 (s, 1H, Ph-NH-CO-), 7.83-7.17 (m, 9H, ArH), 6.35 (s, 2H, -NH_2), 5.00 (s, 1H, CH-Ph), 3.86 (s, 1H, NH), 1.73 (s, 3H, -CH_3). MS: $(M)^+$ 380.12 at m/z. Anal. calcd. (%) for $C_{19}H_{17}ClN_6O$: C, 59.92; H, 4.50; N, 22.07; found (%): C, 59.88; H, 4.61; N, 22.18.

2d: IR (KBr, $\nu_{max,}$ cm^{-1}): 3400 (N-H), 3100 (C…C of aromatic ring), 1693 (C=O), 1577 (C=N), 1461 (N-N), 1261 (C-N), 657 (C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 9.93 (s, 1H, Ph-NH-CO-), 7.77-7.28 (m, 9H, ArH), 6.41 (s, 2H, -NH_2), 4.93 (s, 1H, CH-Ph), 3.97 (s, 1H, NH), 1.78 (s, 3H, -CH_3). MS: $(M)^+$ 380.12 at m/z. Anal. calcd. (%) for $C_{19}H_{17}ClN_6O$: C, 59.92; H, 4.50; N, 22.07; found (%): C, 59.95; H, 4.59; N, 22.00.

2e: IR (KBr, $\nu_{max,}$ cm^{-1}): 3400 (N-H), 3112 (C…C of aromatic ring), 1700 (C=O), 1592 (C=N), 1458 (N-N), 1261 (C-N). ^{1}H NMR ($CDCl_3$, δ ppm): 11.75 (s, 1H, -OH), 9.68 (s, 1H, Ph-NH-CO-), 7.80-7.22 (m, 9H, ArH), 6.35 (s, 2H, -NH_2), 5.00 (s, 1H, CH-Ph), 3.86 (s, 1H, NH), 1.73 (s, 3H, -CH_3). MS: $(M)^+$ 362.15 at m/z. Anal. calcd. (%) for $C_{19}H_{18}N_6O_2$: C, 62.97; H, 5.01; N, 23.19; found (%): C, 63.22; H, 4.97; N, 22.77.

2f: IR (KBr, $\nu_{max,}$ cm^{-1}): 3422 (N-H), 3110 (C…C of aromatic ring), 1690 (C=O), 1586 (C=N), 1461 (N-N), 1257 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 11.61 (s, 1H, -OH), 9.60 (s, 1H, Ph-NH-CO-), 7.71-7.30 (m, 9H, ArH), 6.30 (s, 2H, -NH_2), 5.16 (s, 1H, CH-Ph), 3.98 (s, 1H, NH), 1.52 (s, 3H, -CH_3). MS: $(M)^+$ 362.15 at m/z. Anal. calcd. (%) for $C_{19}H_{18}N_6O_2$: C, 62.97; H, 5.01; N, 23.19; found (%): C, 62.92; H, 5.11; N, 22.93.

2g: IR (KBr, $\nu_{max,}$ cm^{-1}): 3410 (N-H), 3120 (C…C of aromatic ring), 1721 (C=O), 1600 (C=N), 1453 (N-N), 1254 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 11.50 (s, 1H, -OH), 9.58 (s, 1H, Ph-NH-CO-), 7.86-7.25 (m, 9H, ArH), 6.20 (s, 2H, -NH_2), 4.91 (s, 1H, CH-Ph), 3.91 (s, 1H, NH), 1.70 (s, 3H, -CH_3). MS: $(M)^+$ 362.15 at m/z. Anal. calcd. (%) for $C_{19}H_{18}N_6O_2$: C, 62.97; H, 5.01; N, 23.19; found (%): C, 62.88; H, 5.19; N, 22.86.

General method of preparation of 2-(4-Aminopiperidin-1-yl)-5-methyl-*N*-phenyl-7-substitutedphenyl-4,7-dihydro (1,2,4) triazolo (1,5-a)-6-carboxamidopyrimidines (3a-g)

A reaction mixture of compound 2a-g (0.01 mol) and 4-tetrahydro-2*H*-pyran-4-amine (0.01 mol) prepared in N, N-dimethylformamide stirred for 20 minutes at RT followed by refluxing for 3-5 hr. On completion of reaction, excess of solvent distilled away under reduced pressure, residue poured on crushed ice, filtered, washed, dried and recrystallized with appropriate solvents to yield compounds 3a-g.

3a: IR (KBr, $\nu_{max,}$ cm^{-1}): 3380 (N-H), 3100 (C…C of aromatic ring), 1682 (C=O), 1580 (C=N), 1473 (N-N), 1240 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 9.90 (s, 1H, Ph-NH-CO-), 7.81-7.16 (m, 10H, ArH), 5.90 (s, 1H, CH-Ph), 4.88 (s, 2H, -NH_2), 3.70 (s, 1H, NH), 2.75-2.53 (t, 9H, -N-CH_2-), 1.70 (s, 3H, -CH_3). MS: $(M)^+$ 429.23 at m/z. Anal. calcd. (%) for $C_{24}H_{27}N_7O$: C, 67.11; H, 6.34; N, 22.83; found (%): C, 66.98; H, 6.24; N, 23.00.

3b: IR (KBr, $\nu_{max,}$ cm^{-1}): 3352 (N-H), 3070 (C…C of aromatic ring), 1700 (C=O), 1610 (C=N), 1466 (N-N), 1270 (C-N), 678 (C-Cl). ^1H NMR ($CDCl_3$, δ ppm): 9.55 (s, 1H, Ph-NH-CO-), 7.90-7.39 (m, 9H, ArH), 5.60 (s, 2H, -NH_2), 4.75 (s, 1H, CH-Ph), 3.51 (s, 1H, NH), 2.62-2.48 (t, 9H, -N-CH_2-), 1.61 (s, 3H, -CH_3). MS: $(M)^+$ 463.19 at m/z. Anal. calcd. (%) for $C_{24}H_{26}ClN_7O$: C, 62.13; H, 5.65; N, 21.13; found (%): C, 61.96; H, 5.55; N, 21.25.

3c: IR (KBr, $\nu_{max,}$ cm^{-1}): 3375 (N-H), 3083 (C…C of aromatic ring), 1690 (C=O), 1594 (C=N), 1458 (N-N), 1261 (C-N), 670 (C-Cl). ^1H NMR ($CDCl_3$, δ ppm): 9.34 (s, 1H, Ph-NH-CO-), 7.86-7.21 (m, 9H, ArH), 5.86 (s, 2H, -NH_2), 4.64 (s, 1H, CH-Ph), 3.63 (s, 1H, NH), 2.70-2.55 (t, 9H, -N-CH_2-), 1.65 (s, 3H, -CH_3). MS: $(M)^+$ 463.19 at m/z. Anal. calcd. (%) for $C_{24}H_{26}ClN_7O$: C, 62.13; H, 5.65; N, 21.13; found (%): C, 62.10; H, 5.56; N, 20.94

3d: IR (KBr, $\nu_{max,}$ cm^{-1}): 3367 (N-H), 3092 (C…C of aromatic ring), 1688 (C=O), 1602 (C=N), 1471 (N-N), 1257 (C-N), 683 (C-Cl). ^1H NMR ($CDCl_3$, δ ppm): 9.71 (s, 1H, Ph-NH-CO-), 7.80-7.24 (m, 9H, ArH), 5.74 (s, 2H, -NH_2), 4.71 (s, 1H, CH-Ph), 3.60 (s, 1H, NH), 2.75-2.58 (t, 9H, -N-CH_2-), 1.56 (s, 3H, -CH_3). MS: $(M)^+$ 463.19 at m/z. Anal. calcd. (%) for $C_{24}H_{26}ClN_7O$: C, 62.13; H, 5.65; N, 21.13; found (%): C, 62.04; H, 5.66; N, 21.22

3e: IR (KBr, $\nu_{max,}$ cm^{-1}): 3371 (N-H), 3088 (C…C of aromatic ring), 1696 (C=O), 1590 (C=N), 1466 (N-N), 1272 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 10.31 (s, 1H, -OH), 9.43 (s, 1H, Ph-NH-CO-), 7.75-7.20 (m, 9H, ArH), 5.61 (s, 2H, -NH_2), 4.59 (s, 1H, CH-Ph), 3.54 (s, 1H, NH), 2.65-2.45 (t, 9H, -N-CH_2-), 1.40 (s, 3H, -CH_3). MS: $(M)^+$ 445.22 at m/z. Anal. calcd. (%) for $C_{24}H_{27}N_7O_2$: C, 64.70 H, 6.11; N, 22.01; found (%): C, 64.87; H, 6.20; N, 22.12.

3f: IR (KBr, $\nu_{max,}$ cm^{-1}): 3410 (N-H), 3040 (C…C of aromatic ring), 1732 (C=O), 1615 (C=N), 1475 (N-N), 1291 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 10.54 (s, 1H, -OH), 9.54 (s, 1H, Ph-NH-CO-), 7.69-7.23 (m, 9H, ArH), 5.70 (s, 2H, -NH_2), 4.48 (s, 1H, CH-Ph), 3.24 (s, 1H, NH), 2.62-2.40 (t, 9H, -N-CH_2-), 1.33 (s, 3H, -CH_3). MS: $(M)^+$ 445.22 at m/z. Anal. calcd. (%) for $C_{24}H_{27}N_7O_2$: C, 64.70 H, 6.11; N, 22.01; found (%): C, 64.55; H, 6.05; N, 22.21.

3g: IR (KBr, $\nu_{max,}$ cm^{-1}): 3388 (N-H), 3111 (C…C of aromatic ring), 1762 (C=O), 1578 (C=N), 1433 (N-N), 1279 (C-N). ^1H NMR ($CDCl_3$, δ ppm): 10.76 (s, 1H, -OH), 9.41 (s, 1H, Ph-NH-CO-), 7.70-7.35 (m, 9H, ArH), 5.90 (s, 2H, -NH_2), 4.80 (s, 1H, CH-Ph), 3.41 (s, 1H, NH), 2.56-2.36 (t, 9H, -N-CH_2-), 1.29 (s, 3H, -CH_3). MS: $(M)^+$ 445.22 at m/z. Anal. calcd. (%) for $C_{24}H_{27}N_7O_2$: C, 64.70 H, 6.11; N, 22.01; found (%): C, 64.77; H, 6.15; N, 21.93.

RESULTS AND DISCUSSION

Chemistry

By using conventional condensation reaction of 3-oxo-N-phenylbutanamide with 4*H*-1,2,4-triazole-3,5-diamine and different substituted aromatic aldehydes yielded compound 2-amino-5-methyl-*N*,7-diphenyl-4,7-dihydro (1,2,4) triazolo (1,5-a)-6-carboxamidopyrimidines i.e. 2a-g. Reaction of 2a-g and 4- tetrahydro-2*H*-pyran-4-amine 2-(4-Aminopiperidin-1-yl)-5-methyl-*N*-phenyl-7-substitutedphenyl-4,7-dihydro (1,2,4) triazolo (1,5-a)-6-carboxamidopyrimidines (3a-g). All these pyrimidine mimics were purified by crystallisation and also column chromatography with appropriate eluents. These decontaminated target molecules characterised by using elemental, I.R., mass and ^1H-NMR spectral techniques.

Pharmacology

Some 6-substituted carboxamidopyrimidines 2a-g and 3a-g were found to claim significant antibacterial as well as antifungal spectrum against the elect panel of pathogens. Among the series of 2a-g compounds; derivative 2b showed good while 2a went poorest antimicrobial inhibition, inhibitory property was recorded in order of 2b > 2c > 2d > 2e > 2g > 2f > 2a. On the other side in series antimicrobial spectrum chronicled as 3b > 3c > 3d > 3e > 3f > 3g > 3a. In the series of 3a-g, compound 3b showed promising inhibition and 3a weaker potential.

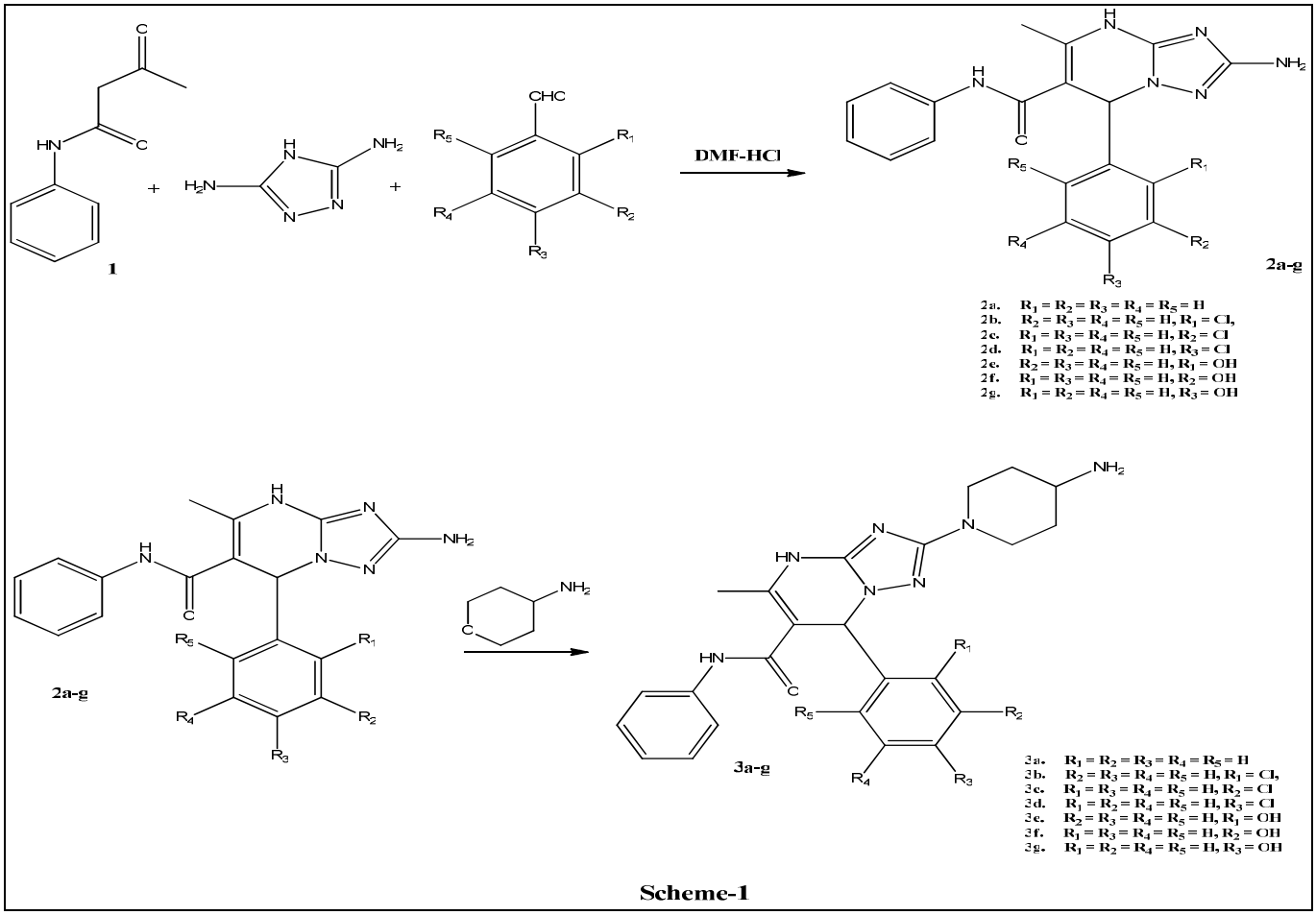
Insecticidal activity of derivatives 2a-g and 3a-g; compounds 3a-g exhibited better potential while compound 2a was found inactive. Among the 3a-g, 3c was found more active against the used cockroaches.

During anthelmintic activity of group of compounds 2a-g, compound 3d showed good but compound 2a claimed no activity. Among 3a-g, derivative 3d showed significant potential than that of any other compounds.

CONCLUSION

In the current study 14 substituted carboxamidopyrimidines synthesised in optimum amount and evaluated for different biological activity viz. antibacterial, antifungal, insecticidal and anthelmintic. Comparative pharmacological evaluation of these tested compounds revealed that halogen substitution was more beneficial than hydroxy substitution.

On the basis of S.A.R., piperidinyl substitution enhanced biological spectrum which was further supported by halo substitution. 2-chlorosubstitution bearing carboxamidopyrimidine derivatives caused better antimicrobial activity. 3-chlororo substituted carboxamidopyrimidines displayed remarkable insecticidal activity. 4-chlororo substituted carboxamidopyrimidines claimed milder insecticidal activity.



Scheme-1

Table 1: Antimicrobial screening data.

Antibacterial activity (mm)				**Antifungal activity** (mm)		
Compound	*S. aureus*	*E.coli*	*K. pnemoniae*	*A. fumigatus*	*C. crusei*	*C. glabrata*
2a.	-	-	-	05	-	-
2b.	12	10	14	08	08	06
2c.	10	10	12	06	08	05
2d.	08	06	08	06	-	-
2e.	05	08	08	06	-	-
2f.	05	05	06	05	-	-
2g.	08	08	06	08	-	-
3a.	-	08	10	08	06	-
3b.	14	16	18	16	12	12
3c.	14	14	16	12	10	08
3d.	12	10	12	10	10	06
3e.	12	14	14	12	10	10
3f.	10	12	10	10	08	08
3g.	08	10	10	08	08	06
Ampicillin trihydrate	16	20	20	-	-	-
Fluconazole	-	-	-	20	15	15
DMF (control)	-	-	-	-	-	-

-: means no activity

Table 2: Insecticidal activity at two different concentrations (KD value in min.)

Compound	Time (min.)	
	1%	2%
2a.	-	-
2b.	14	12
2c.	16	14
2d.	19	14
2e.	18	12
2f.	20	16
2g.	20	17
3a.	20	18
3b.	10	09
3c.	10	07
3d.	14	10
3e.	16	12
3f.	12	10
3g.	14	12
Cypermetrhin	07	05

- : means no activity.

Table 3 : Anthelmintic activity of 2-substituted benzimidazoles against *Pheretima posthuma* (paralytic and lethal time in min.)

Compound	Paralytic Time (min.)	Lethal Time (min.)
2a.	-	-
2b.	14	18
2c.	15	20
2d.	12	16
2e.	18	22
2f.	20	28
2g.	18	25
3a.	20	30
3b.	12	16
3c.	12	17
3d.	10	14
3e.	14	16
3f.	16	20
3g.	18	25
Abendazole	05	08

- : means no activity.

Acknowledgement

Authors are thankful to Dr. K.P. Singh (Chairman) and Dr. Harsh Kumar Daulat (Secretary) for their support during the synthetic lab work.

REFERENCES

Adetunji, C.O.; Oloke, J.K.; Bello, O.M.; Pradeep, M. and Jolly, R.S. (2019). Innovation, Isolation, structural elucidation and bioherbicidal activity of an eco-friendly bioactive 2-(hydroxymethyl) phenol, from *Pseudomonas aeruginosa* (C1501) and its ecotoxicological evaluation on soil. *Environ. Technol. Innov*. 13, 304–317.

Antimicrobial resistance (2021). WHO, https://www.who.int/health-topics/antimicrobial-resistance.

Ashok, D.; Gundu, S.; Aamate, V.K.; Devulapally, M.G.; Bathini, R. and Manga, V. (2018). Dimers of coumarin 1,2,3-triazole hybrids bearing alkyl spacer: Design, microwave-assisted synthesis, molecular docking and evaluation as antimycobacterial and antimicrobial agents. *J. Mol. Struct.,* 1157: 312–321.

Bahadur, S.; Verma, S.; Prasad, S.; Madane, A.; Maurya, S.; Gaurav, V.V. and Sihag, S.J. (2015). Eco-friendly weed management for sustainable crop production-A review. *J. Crop Weed*, 11: 181–189.

Baker, B.P.; Benbrook, C.M.; Groth, E. and Benbrook, K.L. (2002). Pesticide residues in conventional, integrated pest management (IPM) grown and organic foods: insights from three U.S. data sets. *Food Addit. Contam.,* 19: 427–46.

Balzarini, J. and McGuigan, C. (2002). Bicyclic pyrimidine nucleoside analogues (BCNAs) as highly selective and potent inhibitors of varicella-zoster virus replication.*J. Antimicrob. Chemother.,* 7, 50(1): 5-9.

Bayrak, H.; Demirbas, A.; Demirbas, N. and Alpay-Karaoglu, S. (2009). Synthesis of some new 1,2,4-triazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities. *Eur. J. Med. Chem.,* 44: 1057–1066.

Brun, T.; Rabuske, J.E.; Confortin, T.C.; Luft, L.; Todero, I.; Fischer, M.; Zabot, G.L. and Mazutti, M.A. (2020). Weed control by metabolites produced from Diaportheschini. *Environ. Technol*. 1–26.

Chaudhary, N.; Dubey, R. and Panwar, H. (2014). Designing, synthesis and pharmacology of some novel 4-{4-(4-bromobenzyliden) amino} piperidin-1-yl)-5-aryl-3-thiol-4H-1,2,4-triazole. *Der Pharma Chemica*, 6(1): 115-119.

Coe, J.W.; Fliri, A.F.J.; Kaneko, T. and Larson, E.R. (1996). Pyrimidine derivatives enhancing antitumour activity. *U.S. Patent*, 5, 491, 234.

Collins, A.H. (1976). Microbiological methods, Butterworth, London, UK, 8th edn. 2: 136-140.

Cruickshank, R.; Duguid, J.P.; Marion, B.P. and Swain R.H. (1975). A medicinal microbiology, vol. 2, 12th edn. Churchill Livingstone, London, 2: 196–202.

Demirbas, A.; Sahin, D.; Demirbas, N. and Alpay-Karaoglu, S. (2009). Synthesis of some new 1,3,4-thiadiazol-2-ylmethyl-1,2,4-triazole derivatives and investigation of their antimicrobial activities. *Eur. J. Med. Chem.,* 44: 2896–2903.

Food and Agriculture Organization of the United Nations (FAO). 2020, 8.

Food and Agriculture Organization of the United Nations (FAO). 2020. Recommendations for *Improved Weed Management*. Available online: www.fao.org/3/a0884e/a0884e.pdf.

Gama, F.H.S.; de Souza, R.O.M.A. and Garden, S.J. (2015). An efficient green protocol for the preparation of acetoacetamides and application of the methodology to a one-pot synthesis of Biginellidihydropyrimidines. Expansion of dihydropyrimidine topological chemical space. *Royal Soc. Chem. Adv*. 5: 70915-70928.

Ganie, Z.A.; Obrigawitch, T.; Kang, I.H.; Copeland, D.; Gutteridge, S.; May, J.; Schrage, B.; Albright, R. and Chandi, A. (2020). An outlook of FMC's current and future herbicide-resistance management strategies. *Pest Manag. Sci*., 77: 1559–1563.

Hichri, F.; Omri, A.; Hossan, A.S.M. and Ben, J.H. (2019). Alpha-Glucosidase and Amylase Inhibitory Effects of Eruca Vesicaria Subsp. Longirostris Essential Oils: Synthesis of New 1,2,4-Triazole-Thiol Derivatives and 1,3,4-Thiadiazole with Potential Inhibitory Activity. *Pharm. Biol.*, 564–570.

Hickey, L.T.; Hafeez, A.N.; Robinson, H.; Jackson, S.A.; Leal-Bertioli, S.C.; Tester, M.; Gao, C.; Godwin, I.D.; Hayes, B.J. and Wulff, B.B. (2019). Breeding crops to feed 10 billion. *Nat. Biotechnol*. 37: 744–754.

Kaproń, B.; Łuszczki, J.J.; Siwek, A.; Karcz, T.; Nowak, G.; Zagaja, M.; Andres-Mach, M.; Stasiłowicz, A.; Cielecka-Piontek, J. and Kocki, J. (2020). Preclinical Evaluation of 1,2,4-Triazole-Based Compounds Targeting Voltage-Gated Sodium Channels (VGSCs) as Promising Anticonvulsant Drug Candidates. *Bioorg. Chem.*, 94: 103355.

Khanage, S.G.; Raju, A.; Mohite, P.B. and Pandhare, R.B. (2013). Analgesic Activity of Some 1,2,4-Triazole Heterocycles Clubbed with Pyrazole, Tetrazole, Isoxazole and Pyrimidine. *Adv. Pharm. Bull.,* 3: 13–18.

Kompis, I. and Wick, A. (1977). Synthese 4-halogensubstituierten analogen von trimethoprim. *Helvetica Chimica Acta.,* 60(8): 3025–3034.

Kumar, A.; Sharma, S.; Archana, Bajaj, K.; Sharma, S.; Panwar, H.; Singh, T. and Srivastava, V.K. (2003). Some new 2, 3, 6-trisubstituted quinazolinones as potent anti-inflammatory, analgesic and COX-II inhibitors. *Bioorg. Med. Chem*., 11(23): 5293-5299.

Lee, H.W.; Kim, B.Y.; Ahn, J.B.; Kang, S.K.; Lee, J.H.; Shin, J.S.; Ahn, S.K.; Lee, S.J. and Yoon, S.S. (2005). Molecular design, synthesis, hypoglycemic and hypolipidemic activities of novel pyrimidine derivatives having thiazolidinedione. *Eur. J. Med. Chem.,* 7, 40(9): 862-74.

Li, S.M.; Tsai, S.E.; Chiang, C.Y.; Chung, C.Y.; Chuang, T.J.; Tseng, C.C.; Jiang, W.P.; Huang, G.J.; Lin, C.Y. and Yang, Y.C. (2020). New Methyl 5-(Halomethyl)-1-Aryl-1H-1,2,4-Triazole-3-Carboxylates as Selective COX-2 Inhibitors and Anti-Inflammatory Agents: Design, Synthesis, Biological Evaluation, and Docking Study. *Bioorg. Chem.,* 104: 104333.

Nirmal, S.A.; Malwadkar, G. and Laware, R.B. (2007). Anthelmintic activity of Pongamia glabra Songlanakarin. *J. Sci. Technol*., 29: 755-757.

Pannell, D.J.; Tillie, P.; Rodríguez-Cerezo, E.; Ervin, D. and Frisvold, G.B. (2017). Herbicide resistance: Economic and environmental challenges. *Ag. Bio. Forum*, 19, 136–155.

Panwar, H.; Chaudhary, N. and Singh, S. (2012). Antimicrobial evaluation and synthesis of 3,10-disubstituted-6,13-(bis(5-aryl-3-mercapto-1,2,4-triazolyl) dipiperazino)-bis(s-triazolo-(3,4-b)-1,3,4-thiadiazino-(5,6-b;5',6'-e) cyclohexa-1,4-dienes. *J. Chem. Soc. Pak*., 34(2): 457-461.

Panwar, H.; Chaudhary, N.; Dubey, R. and Ram, T. (2013). Quinolin-6-amines: Synthesis and biological evaluation. *Indonesian J. Chem.*, 13(3): 185-192.

Panwar, H.; Chaudhary, N.; Singh, S. and Chawla, A. (2011). Studies on Some Bioactive 1, 1-Bis (2-benzylidene-5-aryliden-1,3-thiadiazolidin-4-one) cyclopropane. *J. Korean Chem. Soc*., 55(6): 994-999.

Panwar, H.; Singh, S. and Chaudhary, N. (2011). Sydnone derivatives a synthons for novel mesoionic compounds. Synthesis, characterization and antimicrobial evaluation of some 2-(4`-substituted anilinosydon-3`-yl)-1, 3, 4-thiadiazino (6,5-b) indoles. *Ind. J. Chem*., 11 (3): 201-206.

Panwar, H.; Verma, R.S.; Srivastava, V.K. and Kumar, A. (2006). Synthesis of some substituted azetidinonyl and thiazolidinonyl 1, 3, 4-thiadiazino (6,5-b)indoles as prospective antimicrobial agents. *Ind. J. Chem*., 45B: 2099-2104.

Phatak, P.S.; Bakale, R.D.; Dhumal, S.T.; Dahiwade, L.K.; Choudhari, P.B.; Krishna, V.S.; Sriram, D. and Haval, K.P. (2019). Synthesis, antitubercular evaluation and molecular docking studies of phthalimide bearing 1,2,3-triazoles. *Synth. Commun,* 49: 2017–2028.

Pogaku, V.; Krishna, V.S.; Balachandran, C.; Rangan, K.; Sriram, D.; Aoki, S. and Basavoju, S. (2019). The design and green synthesis of novel benzotriazoloquinolinylspirooxindolopyrrolizidines: Antimycobacterial and antiproliferative studies. *New J. Chem.,* 43: 17511–17520.

Pussemier, L.; Larondelle, Y.; Van, P.C. and Huyghebaert, A. (2006). Chemical safety of conventionally and organically produced foodstuffs: a tentative comparison under Belgian conditions. *Food Control.,* 17: 14–21.

Roth, B. and Cheng, C.C. (1982). Recent progress in the medicinal chemistry of 2,4-diaminopyrimidines.*Prog. Med. Chem.*, 19: 269-331.

Shaikh, M.H.; Subhedar, D.D.; Nawale, L.; Sarkar, D.; Khan, F.A.K.; Sangshettic, J.N. and Shingate, B.B. (2015).

1,2,3-Triazole derivatives as antitubercular agents: Synthesis, biological evaluation and molecular docking study. *Med. Chem. Commun.,* 6: 1104–1116.

Sharma, P.; Rane, N. and Gurram, V.K. (2004). Synthesis and QSAR studies of pyrimido (4,5-d) pyrimidine-2,5-dione 57derivatives as potential antimicrobial agents. *Bioorg*. *Med. Chem. Lett.,* 16, 14(16): 4185-4190.

Strzelecka, M. and Świątek, P. (2021). 1,2,4-Triazoles as Important Antibacterial Agents, *Pharmaceuticals,* 14, 3: 224.

Tambe, V.D.; Nirmal, S.A.; Jadhav, R.S.; Ghogare, P.B.; Bhalke, R.D.; Girme, A.S. and Bhamber, S. (2006). Anthelmintic activity of Wedeliatrilobata leaves. *Ind. J. Nat. Prod.*, 22: 27.

The Interagency Coordination Group on Antimicrobial Resistance (IACG). 2019. No time to wait: securing the future from drug-resistant infections.

Thorn, G.W.; Adams, R.D. and Petersdrof, R.G. (1977). Harrison's Principles of Internal Medicine, 1088.

Varadraj, P.; Ganavalli, A. and Narayanshetty, N.K. (2018). Antifungal Resistance in Dermatology, *Indian J. Dermatol*., 63(5): 361–368.

Vilgar, Z. (1984). Atlas of Medical Parasitology, 216.

Werkheiser, W.C. (1961). Specific binding of 4-amino folic acid analogues by folic acid reductase. *The Journal of Biological Chemistry,* 236(3): 888–893.