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**Der Pharma Chemica, 2014, 6(1):115-119**
*(http://derpharmachemica.com/archive.html)*

**ISSN 0975-413X**
**CODEN (USA): PCHHAX**

# Designing, synthesis and pharmacology of some novel 4-{4-(4-bromobenzyliden)amino}piperidin-1-yl)-5-aryl-3-thiol-*4H*-1,2,4-triazole

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## ABSTRACT

*In the current study design, synthesis and biological evaluation of several substituted 1,2,4-triazoles have been reported. Structures of the synthesized substituted triazoles were characterized by IR, $^1$H-NMR, Mass and elemental analysis (C, H, N). Synthesised triazoles were screened for antibacterial, antifungal and insecticidal activities.*

**Keywords**: Antibacterial, antifungal, insecticidal, 1,2,4-triazoles.

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## INTRODUCTION

1,2,4-triazole containing ring systems explored a wide variety of therapeutically interesting drug candidature including antiseptic, analgesic, anti-convulsant, antibiotic [1], antiallergic [1], anti-inflammatory [1-10,13], diuretic [1,5,8], fungicidal [3,4,10-13], insecticidal [3,10,13], herbicidal [3,10,13], antibacterial [3-6,11,12], antiviral [2-5,7,8,10], antidepressant [2,5,9], antimicrobial [2-5,7,10-12], antitumor [3,6,9-10], antihypertensive [5,8-9], and antimigraine compounds [7]. In addition many triazole drugs are under clinical use, e.g. anastrozole, rizatriptan, nefazodone, vorozole, ribavirin, fluconazole, letrozole and uniconazole, which possess the 1,2,4-triazole moiety as block material. Furthermore triazoles also displayed their versatility in industries as precursors for photosensitive materials as inks and toners [14], polymer chemistry [11], and others [15-16]. In the current study we tried to design, develop some novel 1,2,4-triazole derivatives with the chemical modifications including joined tetrahydro-2*H*-pyran-4-amine and 4-bromo benzaldehyde moieties.

## MATERIALS AND METHODS

All the chemicals used for the preparation of desired derivatives, were obtained from Sisco Research Laboratories (SRL), Mumbai, India; Qualigen Fine Chemicals, Mumbai, India. The melting points of the compounds were determined in open glass capillaries with the help of thermonic melting points apparatus and are uncorrected. The homogeneity of all the newly synthesized compounds was routinely checked by TLC on silica gel G plates and spots were located by using iodine chamber. Elemental analysis was performed in Heraeus CHN rapid analyser. The results were found within the ±0.4% of theoretical values. Infrared spectra were recorded on KBr pellets on a Perkin Elmer system 2000 FT-IR spectrometer and $^1$H NMR spectra on Bruker DPX 200 using TMS as internal standard.

### *Antimicrobial Tests*

All the newly synthesized compounds were screened for their antibacterial and antifungal activity against the clinically isolated and identified microbial strains. The pathogens were obtained from the Department of Pathology, L.L.R.M. Medical College, India. Preliminary antimicrobial susceptibility test for the newly synthesized compounds 3a-f, 4a-f and 5a-b were screened for their antibacterial and antifungal activity. Disk diffusion method [21-22] was used for determination of the preliminary antibacterial activity. While on the other hand, the newly prepared

compounds were screened for their in vitro antifungal activity by the serial plate dilution method [23-24]. Ampicillin trihydrate and fluconazole were used as standard drugs. The inhibitory values of the tested compounds against the tested bacterial and fungal strains were recorded in mm (**Table-1**).

***Insecticidal study***

*Periplaneta americana* was taken for insecticidal study and 1 and 2% acetone solutions of the synthesized 2-substituted benzimidazole derivatives **3a-f** 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. The time of cockroach's death was recorded as knock down (KD) value. Cypermethrin was used as standard drug. At the time of death the antennae of *P. americana* became motionless, the appendages shrunk and folded towards the ventral side and cockroach lay dorsally [25] (**Table-2**).

**Synthesis**

**General preparation of 4-(4-Aminopiperidin-1-yl)-5-aryl-3-thiol-4H-1,2,4-triazole 2a-f**

A dimethylformamide solution of 3-Aryl-4-amino-5-mercapto triazoles [26-29] 1a-f (0.01mol) and tetrahydro-2*H*-pyran-4-amine (0.01 mol) was refluxed for 3-5 h. Excess of solvent was distilled off, residue dumped in ice-water, washed, filtered, dried to afford crude 2a-f. Crude products was recrystallised with appropriate solvents.

***4-(4-Aminopiperidin-1-yl)-5-phenyl-3-thiol-4H-1,2,4-triazole*** **2a:** Yield 68%, mp 159 $^0$C. IR (KBr, $\upsilon_{max}$ cm$^{-1}$): 1678 (C…C of aromatic ring), 1602 (SH), 1556 (C=N), 1520 (N-N), 1304 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.02-2.51 (t, 9H, -N-$CH_2$-$CH_2$-), 4.56 (brs, 2H, $NH_2$), 6.71-7.12 (m, 5H, ArH), 12.63(s, 1H, HS). MS: $[M]^+$ 275.37 at *m/z*. Anal. Calcd for $C_{13}H_{17}N_5S$: C, 56.70; H, 6.22; N, 25.43; found: C, 56.58; H, 6.75; N, 25.45.

**4-(4-Aminopiperidin-1-yl)-5-(2-hydroxy)phenyl-3-thiol-4H-1,2,4-triazole 2b:** Yield 61%, mp 167 $^0$C. IR (KBr, $\upsilon_{max}$ cm$^{-1}$): 1684 (C…C of aromatic ring), 1610 (SH), 1560 (C=N), 1521 (N-N), 1300 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.00-2.59 (t, 9H, -N-$CH_2$-$CH_2$-), 4.50 (brs, 2H, $NH_2$), 6.67-7.05 (m, 4H, ArH), 10.50 (s, 1H, OH), 12.63(s, 1H, HS). MS: $[M]^+$ 291.37 at *m/z*. Anal. Calcd for $C_{13}H_{17}N_5SO$: C, 53.59; H, 5.88; N, 24.04; found: C, 53.57; H, 5.79; N, 24.10.

**4-(4-Aminopiperidin-1-yl)-5-(3-hydroxy)phenyl-3-thiol-4H-1,2,4-triazole 2c:** Yield 64%, mp 154 $^0$C. IR (KBr, $\upsilon_{max}$ cm$^{-1}$): 1682 (C…C of aromatic ring), 1606 (SH), 1555 (C=N), 1524 (N-N), 1305 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.10-2.54 (t, 9H, -N-$CH_2$-$CH_2$-), 4.60 (brs, 2H, $NH_2$), 6.70-7.00 (m, 4H, ArH), 10.44 (s, 1H, OH), 12.52(s, 1H, HS). MS: $[M]^+$ 275.37 at *m/z*. Anal. Calcd for $C_{13}H_{17}N_5SO$: C, 53.59; H, 5.88; N, 24.04; found: C, 53.57; H, 5.79; N, 24.10.

**4-(4-Aminopiperidin-1-yl)-5-(4-hydroxy)phenyl-3-thiol-4H-1,2,4-triazole 2d:** Yield 56%, mp 139 $^0$C. IR (KBr, $\upsilon_{max}$ cm$^{-1}$): 1680 (C…C of aromatic ring), 1606 (SH), 1564 (C=N), 1526 (N-N), 1303 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.04-2.67 (t, 9H, -N-$CH_2$-$CH_2$-), 4.53 (brs, 2H, $NH_2$), 6.59-7.02 (m, 4H, ArH), 10.55 (s, 1H, OH), 12.60(s, 1H, HS). MS: $[M]^+$ 291.37 at *m/z*. Anal. Calcd for $C_{13}H_{17}N_5SO$: C, 53.59; H, 5.88; N, 24.04; found: C, 53.61; H, 5.90; N, 24.00.

**4-(4-Aminopiperidin-1-yl)-5-(2-chloro)phenyl-3-thiol-4H-1,2,4-triazole 2e:** Yield 52%, mp 172 $^0$C. IR (KBr, $\upsilon_{max}$ cm$^{-1}$): 1685 (C…C of aromatic ring), 1608 (SH), 1558 (C=N), 1523 (N-N), 1309 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.07-2.55 (t, 9H, -N-$CH_2$-$CH_2$-), 4.51 (brs, 2H, $NH_2$), 6.78-7.20 (m, 4H, ArH), 12.48 (s, 1H, HS). MS: $[M]^+$ 309.82 at *m/z*. Anal. Calcd for $C_{13}H_{16}N_5SCl$: C, 50.40; H, 5.21; N, 22.60; found: C, 50.44; H, 5.25; N, 22.62.

**4-(4-Aminopiperidin-1-yl)-5-(4-chloro)phenyl-3-thiol-4H-1,2,4-triazole 2f:** Yield 48%, mp 160 $^0$C. IR (KBr, $\upsilon_{max}$ cm$^{-1}$): 1687 (C…C of aromatic ring), 1605 (SH), 1560 (C=N), 1520 (N-N), 1304 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.00-2.51 (t, 9H, -N-$CH_2$-$CH_2$-), 4.58 (brs, 2H, $NH_2$), 6.68-7.18 (m, 4H, ArH), 12.58 (s, 1H, HS). MS: $[M]^+$ 309.82 at *m/z*. Anal. Calcd for $C_{13}H_{16}N_5SCl$: C, 50.40; H, 5.21; N, 22.60; found: C, 50.38; H, 5.22; N, 22.57.

**General preparation of 4-{4-(4-bromobenzyliden)amino}piperidin-1-yl)-5-aryl-3-thiol-4H-1,2,4-triazole 3a-f**

An ethanolic mixture of compound 2a-f (0.01 mol) and 4-bromobenzaldehyde (0.01 mol) in the presence of few drops of glacial acid was refluxed for 3 hr. On completion of reaction, excess of ethanol was distilled, residue poured on crushed ice and resultant solid was recrystallized from ethanol to yield compounds 3a-f.

***4-{4-(4-bromobenzyliden)amino}piperidin-1-yl)-5-phenyl-3-thiol-4H-1,2,4-triazole*** **3a:** Yield 51%, mp 128 $^0$C. IR (KBr, $\upsilon_{max}$ cm$^{-1}$): 1680 (C…C of aromatic ring), 1615 (SH), 1570 (C=N), 1522 (N-N), 1312 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.12-2.55 (t, 9H, -N-$CH_2$-$CH_2$-), 5.70 (s, 1H, CH-Ar), 6.60-7.50 (m, 8H, ArH), 12.40 (s, 1H, HS).

MS: $[M]^+$ 442.38 at *m/z*. Anal. Calcd for $C_{20}H_{20}N_5SBr$: C, 54.30; H, 4.56; N, 15.83; found: C, 54.51; H, 4.55; N, 15.76.

***4-{4-(4-bromobenzyliden)amino}piperidin-1-yl)-5-(2-hydroxy)phenyl-3-thiol-4H-1,2,4-triazole*** **3b:** Yield 51%, mp 128 $^0$C. IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 1682 (C…C of aromatic ring), 1613 (SH), 1574 (C=N), 1524 (N-N), 1310 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.14-2.57 (t, 9H, -N-$CH_2$-$CH_2$-), 5.67 (s, 1H, CH-Ar), 6.65-7.52 (m, 8H, ArH), 10.42 (s, 1H, OH), 12.49 (s, 1H, HS). MS: $[M]^+$ 458.37 at *m/z*. Anal. Calcd for $C_{20}H_{20}N_5SBrO$: C, 52.41; H, 4.40; N, 15.28; found: C, 52.50; H, 4.42; N, 15.27.

***4-{4-(4-bromobenzyliden)amino}piperidin-1-yl)-5-(3-hydroxy)phenyl-3-thiol-4H-1,2,4-triazole*** **3c:** Yield 54%, mp 144 $^0$C. IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 1688 (C…C of aromatic ring), 1607 (SH), 1568 (C=N), 1521 (N-N), 1319 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.04-2.49 (t, 9H, -N-$CH_2$-$CH_2$-), 5.64 (s, 1H, CH-Ar), 6.57-7.44 (m, 8H, ArH), 10.48 (s, 1H, OH), 12.56 (s, 1H, HS). MS: $[M]^+$ 458.37 at *m/z*. Anal. Calcd for $C_{20}H_{20}N_5SBrO$: C, 52.41; H, 4.40; N, 15.28; found: C, 52.47; H, 4.48; N, 15.31.

***4-{4-(4-bromobenzyliden)amino}piperidin-1-yl)-5-(4-hydroxy)phenyl-3-thiol-4H-1,2,4-triazole*** **3d:** Yield 48%, mp 161 $^0$C. IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 1685 (C…C of aromatic ring), 1617 (SH), 1566 (C=N), 1520 (N-N), 1313 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.11-2.46 (t, 9H, -N-$CH_2$-$CH_2$-), 5.60 (s, 1H, CH-Ar), 6.68-7.40 (m, 8H, ArH), 10.51 (s, 1H, OH), 12.42 (s, 1H, HS). MS: $[M]^+$ 458.37 at *m/z*. Anal. Calcd for $C_{20}H_{20}N_5SBrO$: C, 52.41; H, 4.40; N, 15.28; found: C, 52.50; H, 4.42; N, 15.27.

***4-{4-(4-bromobenzyliden)amino}piperidin-1-yl)-5-(2-chloro)phenyl-3-thiol-4H-1,2,4-triazole*** **3e:** Yield 50%, mp 144 $^0$C. IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 1690 (C…C of aromatic ring), 1620 (SH), 1570 (C=N), 1526 (N-N), 1318 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.05-2.49 (t, 9H, -N-$CH_2$-$CH_2$-), 5.52 (s, 1H, CH-Ar), 6.71-7.38 (m, 8H, ArH), 12.46 (s, 1H, HS). MS: $[M]^+$ 476.82 at *m/z*. Anal. Calcd for $C_{20}H_{19}N_5SBrCl$: C, 50.38; H, 4.02; N, 16.76; found: C, 50.30; H, 4.14; N, 16.77.

***4-{4-(4-bromobenzyliden)amino}piperidin-1-yl)-5-(4-chloro)phenyl-3-thiol-4H-1,2,4-triazole*** **3f:** Yield 42%, mp 159 $^0$C. IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 1684 (C…C of aromatic ring), 1623 (SH), 1568 (C=N), 1523 (N-N), 1315 (C-N). $^1$H NMR ($CDCl_3$, $\delta$ ppm): 2.15-2.54 (t, 9H, -N-$CH_2$-$CH_2$-), 5.44 (s, 1H, CH-Ar), 6.80-7.43 (m, 8H, ArH), 12.56 (s, 1H, HS). MS: $[M]^+$ 476.82 at *m/z*. Anal. Calcd for $C_{20}H_{19}N_5SBrCl$: C, 50.38; H, 4.02; N, 16.76; found: C, 50.39; H, 4.10; N, 16.68.

## RESULTS AND DISCUSSION

### *Chemistry*

Synthetic strategy is depicted in scheme-**1**. 3-Aryl-4-amino-5-mercapto triazoles and tetrahydro-2*H*-pyran-4-amine were refluxed to furnish 4-(4-aminopiperidin-1-yl)-5-aryl-3-thiol-4H-1,2,4-triazole **2a-f** which react further with 4-bromobenzaldehyde in the presence of glacial acid to yielded 4-{4-(4-bromobenzyliden)amino}piperidin-1-yl)-5-aryl-3-thiol-4H-1,2,4-triazole **3a-f**.

**Table-1: Antimicrobial evaluation of 4-{4-(4-bromobenzyliden) amino} piperidin-1-yl)-5-aryl-3-thiol-4H-1,2,4-triazole 3a-f**

| Comp. | R | Antibacterial activity (mm) | | Antifungal activity | |
|---|---|---|---|---|---|
| | | *S. aureus* | *K. pneumoniae* | *A. fumigatus* | *C. glabrata* |
| 3a. | $C_6H_5$ | - | 5 | - | - |
| 3b. | 2-OH. $C_6H_4$ | 6 | 8 | - | - |
| 3c. | 3-OH. $C_6H_4$ | 8 | 5 | - | - |
| 3d. | 4-OH. $C_6H_4$ | 8 | 6 | - | - |
| 3e. | 2-Cl. $C_6H_4$ | 10 | 12 | 8 | 6 |
| 3f. | 4-Cl. $C_6H_4$ | 15 | 14 | 12 | 10 |
| *Ampicillin trihydrate* | | 16 | 20 | - | - |
| *Fluconazole* | | - | - | 20 | 15 |
| DMF (control) | | - | - | - | - |

*- means no activity.*

### *Pharmacology*

All the prepared derivatives 4-{4-(4-bromobenzyliden)amino}piperidin-1-yl)-5-aryl-3-thiol-4H-1,2,4-triazoles **3a-f** were evaluated for antibacterial, antifunagal and insecticidal activities. *Staphylococcus aureus* and *Klabsiella pneumoniae* used for antibacterial activity. *Aspergillus fumigatus* (plant isolate) and *Candida glabrata* were used for antifungal activity. Insecticidal activity performed against *Periplaneta Americana*. During antimicrobial screening, results revealed that compound **3e** and **3f** showed promising antimicrobial spectrum. Compound **3a** was active only against *K. pneumonia*. Compound **3b** and **3c** inhibited bacterial growth but showed no inhibition against the used

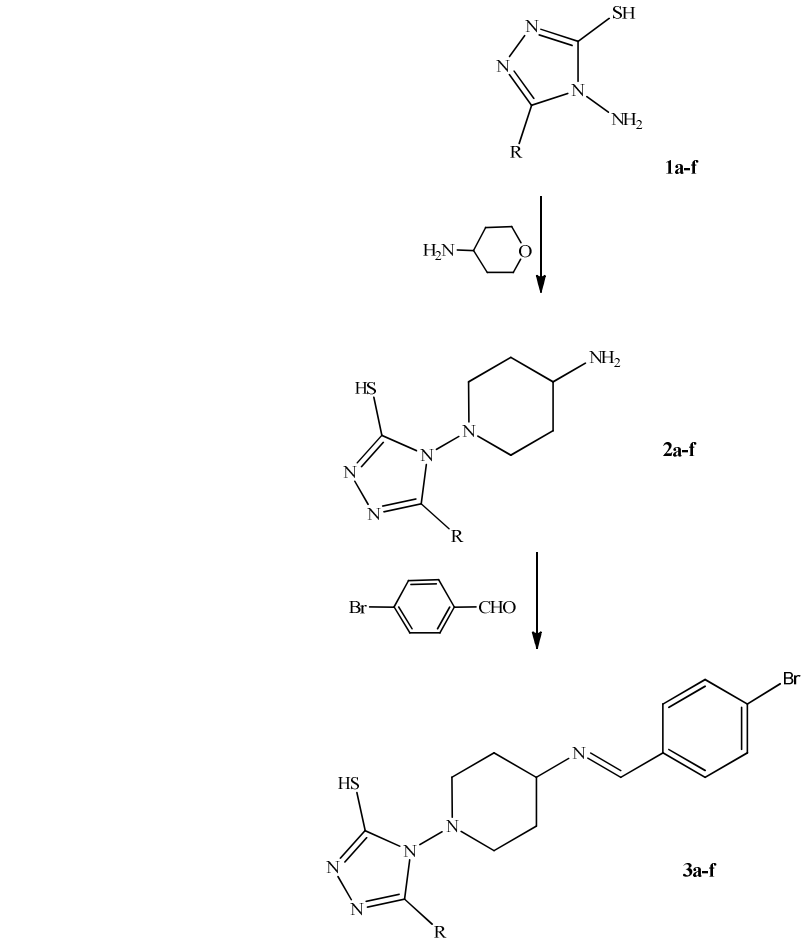
fungal strains. Compound **3d** and **3e** revealed almost equal antimicrobial potential. Compound **3e** and **3f** showed inhibition against the used antimicrobial strains but compound **3f** was the most potent derivative. Compound **3f** demonstrated remarkable activity in comparison to the used microbial strains.

Insecticidal activity results cleared that among the tested compounds **3a-f**, compound **3d** showed better KD values at two different doses- 1% and 2% against *P. americana*. Compound **3f** displayed considerable insecticidal potential in comparison to used standard cypermethrin.

**Table 2: Insecticidal activity of 4-{4-(4-bromobenzyliden) amino} piperidin-1-yl)-5-aryl-3-thiol-4H-1,2,4-triazole 3a-f at two different concentrations (KD value in min.)**

| Comp. | R | Time [min.] | |
|---|---|---|---|
| | | 1% | 2% |
| 3a. | $C_6H_5$ | - | - |
| 3b. | 2-OH. $C_6H_4$ | - | - |
| 3c. | 3-OH. $C_6H_4$ | - | - |
| 3d. | 4-OH. $C_6H_4$ | 25 | 18 |
| 3e. | 2-Cl. $C_6H_4$ | 18 | 1 |
| 3f. | 4-Cl. $C_6H_4$ | 15 | 10 |
| **Cypermethrin** | | 7 | 5 |

*- means no activity.*




**R = $C_6H_5$, 2 -OH.$C_6H_4$, 3-OH.$C_6H_4$, 4-OH.$C_6H_4$, 2-Cl.$C_6H_4$, 4 -Cl.$C_6H$ 4**

**Scheme-1**

## CONCLUSION

On the basis of structure activity relationship, it was found that presence of electron-withdrawing group on the aromatic ring showed remarkable antibacterial and antifungal activity. Among the biologically screened compounds 3a-f only derivative **3e** and **3f** elucidated better biological potency. On the basis of structure-activity relationships (SAR), among the all 1,2,4-triazole derivative 3a-f, 4-chloro phenyl substitution was responsible to enhance the antibacterial and antifungal activity.

**Acknowledgement**
We are thankful for Mr. Brijver Singh, *Chairman* and Dr. Dinesh Chandra Sharma, *Vice chairman*, Neelkanth Institute of Technology, to provide essential support and facilities.

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