Chemistry & Biology Interface, 2018, 8, 5, 269-275

RESEARCH PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

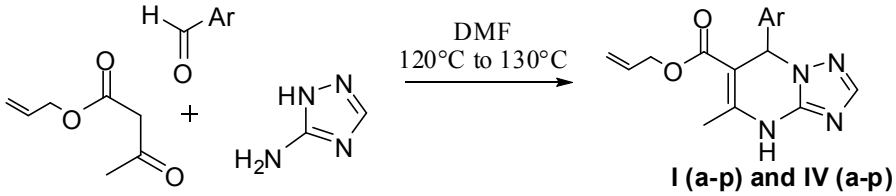
An official Journal of ISCB, Journal homepage; www.cbijournal.com

Synthesis, characterization and biological evolution of some novel derivatives of 1,2,4-triazole

Atul H Makwana[1]*, Alimamad H Malani[2]

Chemistry Department, St. Xavier's College (Autonomous), Navarangpura, Ahmedabad-380009, Gujarat, India
[1]E-mail: makwana_atul@yahoo.com
[2]E-mail: ali_malani@yahoo.com
Received 19 June 2018; Accepted 17 September 2018

Abstract: Azoles are five member heterocyclic moieties with two or more hetero atoms where at least one should be nitrogen. They are generally found in natural sources and there are many drugs available which have azoles moiety in its structure. We have prepared 1,2,4- triazoles which is well known class of triazoles having three nitrogen atoms in the hetero cyclic ring. 1,2,4-triazoles are known for their broad range of therapeutic activities. Structures of newly synthesized triazole derivatives were confirmed by analytical techniques like Infrared Spectroscopy, Nuclear Magnetic Resonance and Mass spectrometry methods. Broth dilution method was used to determine antibacterial and anti-fungal activities of the synthesized compounds.



I (a-p) and IV (a-p)

Keywords: Antibiotics, Biginelli reaction, Biological activity, Multicomponent reaction, 1,2,4-triazole

Introduction:

In today's era the most prescribed drugs are the antibiotic drugs. Due to increased use of several antibiotics drugs, many lives have been saved. Although many antibiotics are available in market, still there is a need of drug with higher activity and simultaneously lesser side effects [1]. 1,2,4-Triazole and its derivatives are found to show various biological activities such as antimicrobial, analgesic, anti-inflammatory, anticancer and antioxidant properties [2-5]. They are also useful as in photosensitive materials [6], as corrosion inhibitors [7] and in synthesis

of several bioactive heterocyclic compounds. Many common medicines available for different diseases are found to containing 1,2,4-triazole as heterocyclic moiety. The examples include Ribavirin which is antiviraldrug, Rizatriptan is used to cure migrain, Estazolam and Alprazolam are anxiolytic, Letrozole and Anastrozole are anticancer drugs. Triazole derivatives found in drugs like Itraconazole, Fluconazole, Posaconazole are useful for the treatment of fungal infections where as Ruficonamide is well known anticonvulsant [8-19].Triazole derivatives also found to possess moderate to good antibacterial and antifungal activities [20]. Many methods are reported for the preparation of bioactive triazole derivatives. One of them is Biginelli reaction which involves condensation of 1,2,4-triazole-5-amine and β-keto ester with different aldehydes. Looking to the pharmacological importance we have synthesized a new series of compounds containing triazole and dihydropyrimidine moieties in one frame work using reported method [21, 22].

Materials and methods:

General: All the chemicals required are obtained from Spectrochem, Finar and Sigma Aldrich. Merck Kieselgel 60 F254 plates were used for TLC. The ^{1}H NMR spectra were recorded in DMSO d6 solution in 5 mm tubes at room temperature, on a BRUKER 400 MHz FT-NMR, with TMS as internal standard. IR Spectra were recorded on SHIMADZU FT-IR 8400 using potassium bromide pallets. Mass spectra were recorded on SHIMADZU QP-2010. The antimicrobial activity was carried out using broth dilution method to determine minimum inhibitory concentration (MIC).

General Procedure for the preparation of compounds Ia-p (Table-1) (Scheme-1):

Allyl-3-oxobutanoate (0.0142 mol), 1H 1,2,4-triazole 5-amine (0.0142 mol) and different aldehydes (0.0142 mol), were taken in round bottom flask followed by the addition of dimethylformamide (DMF) (10 ml) and one drop of H_2SO_4. The reaction mass was heated at 125°C with constant stirring for 1 hour. The progress and completion of the reaction was confirmed by TLC (Mobile Phase 9:1 Methylene dichloride (MDC): Methanol and 1-2 drop of acetic acid). The reaction mixture was then poured in to ice cold water and the solid product formed was filtered. The solid obtained was re-crystallized from acetone or methanol.

As per preparation of triazole by scheme-1, we have also prepared some novel triazole derivatives as per scheme-2 as explained below.

General Procedure for synthesis of phenyl hydrazones (II) (Scheme-2, Step-1):

To a solution of acetophenone (0.065 mol) in 50 mL methanol, phenyl hydrazine (0.065 mol) and glacial acetic acid (2 ml) were added. The resulting solution was stirred for half an hour at room temperature. The precipitates of hydrazone derivatives (II) were filtered and washed with methanol [23].

General Procedure for the preparation of 3-(Aryl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (III) (Scheme-2, Step-2):

Hydrazones (II) (0.022 mol) (prepared in step-1) were reacted with anhydrous DMF (0.022 mol) in the presence of $POCl_3$ (6 ml) at 0°C-5°C. The reaction mixture was then heated at 90-100 °C for 4-5 hours. The resulting mixture was poured in to crushed ice and neutralized with dilute sodium hydroxide. The precipitates obtained were filtered, washed with water and recrystalized from chloroform [23] to form various heterocyclic aldehydes (III a-p).

General Procedure for the preparation of

compounds IV (a-p) (Table-1) (Scheme-2, Step-3):

Allyl-3-oxobutanoate (0.0071 mol), 1*H* 1,2,4-triazole 5-amine (0.0071 mol) and different aldehydes (III (a-p) (0.0071 mol), were taken in a round bottom flask followed by the addition of dimethylformamide (DMF) (10 ml) and one drop of H_2SO_4. The reaction mass was heated at 120°C to 130° C for about one hour with constant stirring. The progress and completion of the reaction was confirmed by TLC (Mobile Phase 9:1 MDC: Me-OH and 1-2 drop of acetic acid). The reaction mixture was then poured in to ice cold water and the solid product formed was filtered. The solid obtained was re-crystallized from acetone or methanol.

Spectral data of some of the synthesized compounds:

Allyl 7-(4-chlorophenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (Ia) IR (cm^{-1}): 740 (Ar C-H bending),1624 (Ar C=C Bending), 1685 (Alkenyl C=C Stretching), 1761 (COOR),3051 (Ar C-H Stretching),NMR(DMSO, 400 MHz) (δ ppm): 2.51 (3H, d, J=1.6),4.48 (2H, m),5.10 (2H, d,d, J=1.6, 8.4),5.80 (1H, m),6.31 (1H, s),7.27 (2H, d, d, J=5.6, 8.4),7.39 (2H, d, d, J=2.0, 8.8), 7.68 (1H,s)10.95 (1H, s), Mass (m/z): (m-1) 330

Allyl 7-(4-bromophenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (Ib):IR (cm^{-1}): 738 (Ar C-H bending),1558 (Ar C=C Bending), 1685 (Alkenyl C=C Stretching), 1762 (COOR),3047 (Ar C-H Stretching),NMR(DMSO, 400 MHz) (δ ppm): 2.50 (3H, s), 4.50 (2H, m), 5.03 (1H, d, J=1.6, 4.2), 5.11 (1H, d, J=1.6, 4.2), 5.78 (1H, m),6.34 (1H, s), 7.12 (2H, d, J=8.4), 7.85 (2H, d, J=8.4), 8.25 (1H, s), 10.90 (1H, s), Mass (m/z): 376

Allyl 7-(4-flourophenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (Ic):IR (cm^{-1}): 740 (Ar C-H bending),1620 (Ar C=C Bending), 1685 (Alkenyl C=C Stretching), 1760 (COOR),3050 (Ar C-H Stretching),NMR(DMSO, 400 MHz) (δ ppm): 2.51 (4H, s),4.48 (2H, t, J=1.64), 5.11 (1H, d,d, J=10, 1.52),5.82 (1H, m), 6.63 (1H, s),7.2 (4H, d, d, J=1.6, 8.4), 7.39 (4H, d,d, J=2.0, 7.6), 7.68 (2H, s),10.90 (1H, s), Mass (m/z): 315

Allyl 7-(3-bromophenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (Ig): IR (cm^{-1}): 737 (Ar C-H bending),1618 (Ar C=C Bending), 1686 (Alkenyl C=C Stretching), 1759 (COOR),3049 (Ar C-H Stretching),NMR(DMSO, 400 MHz) (δ ppm): 2.51 (3H, s), 4.48 (2H, m), 5.09 (2H, t, J=2.8), 5.78 (1H, m), 6.32 (1H, s), 7.22 (1H, d, d, J=1.2, 8.8), 7.29 (1H, t, J=8.8), 7.43 (1H, t, J=3.6), 7.46 (1H, d, t, J=1.6, 10.4), 7.70 (1H, s), 10.97 (1H, s), Mass (m/z): 376.

Allyl-7-[3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl]-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (IVd): IR (cm^{-1}): 740 (Ar C-H bending), 1620 (Ar C=C Bending), 1682 (Alkenyl C=C Stretching), 1745 (COOR), 3050 (Ar C-H Stretching),NMR(DMSO, 400 MHz) (δ ppm):2.40 (3H, s), 4.45 (2H, m), 4.95 (1H, d, d, J=1.6, 8.2), 5.05 (11H, d, d, J=1.6, 8.2), 5.58 (1H, m), 5.66 (1H, s), 6.55 (1H, s), 7.30 (2H,d, 7.2), 7.48 (1H, t, J=8.4),7.91 (5H, t, 9.2), 8.21 (2H, d, 4.5), 8.39 (2H, d, 7.2), 8.64 (1H, s), 10.88 (1H, s), Mass (m/z): 483.

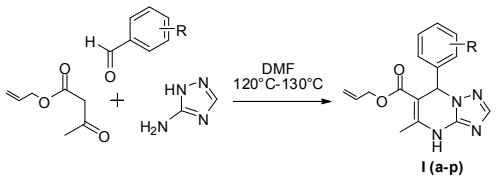
Allyl-7-[3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a] pyrimidine-6-carboxylate (IVn): IR (cm^{-1}): 739 (Ar C-H bending), 1616 (Ar C=C Bending), 1685 (Alkenyl C=C Stretching), 1763 (COOR), 3042 (Ar C-H Stretching), NMR(DMSO, 400 MHz) (δ

ppm):2.50 (3H, s), 3.83 (3H, s), 4.41 (2H, m), 4.95 (2H, q, d, J=1.6, 10.8), 5.59 (1H, q, 11.6), 6.46 (1H, s), 7.07 (2H, d, J=8.8), 7.30 (1H, t, J=7.2), 7.49 (2H, t, J=8.0), 7.72 (1H, d, J=5.2), 7.87 (4H, t, J=7.6), 8.49 (1H, s), 10.80 (1H, s), Mass (m/z): 469.

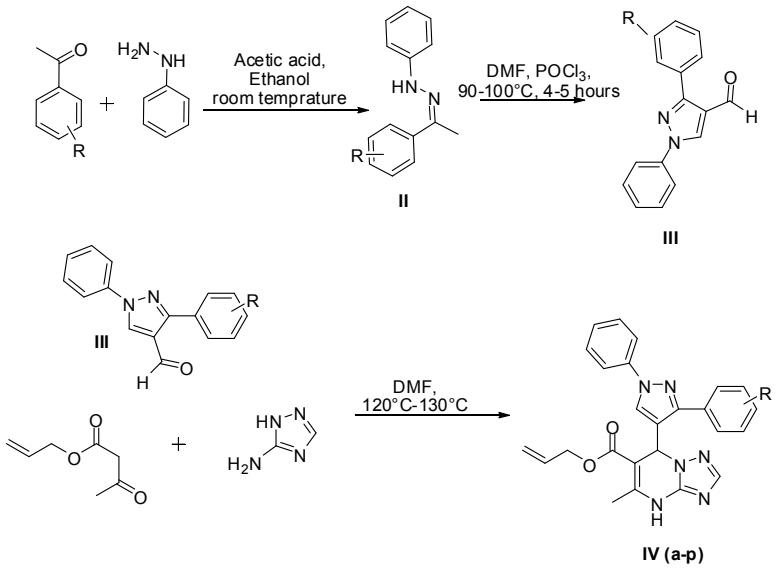
Results and Discussion

In the present work we have prepared some new derivatives of 1,2,4-triazole by Biginelli reaction. The structure of the synthesized compounds were confirmed by IR, ^{1}H NMR and Mass spectra. Compound **Ia** exhibited absorption at 740 cm^{-1} due to aromatic C-H bending, 1624 cm^{-1} due to Ar C=C Bending, 1685 cm^{-1} due alkenyl C=C Stretching, a strong absorption observed at 1761 cm^{-1} carbonyl group etc in IR spectrum. Some of the characteristics signals in ^{1}H NMR of the compound **Ig** are, 2.51 δ ppm 3H corresponds to methyl group, 6.32 δ ppm 1H due to proton attached to ipso carbon of dihydropyrimidine , 10.97 δ ppm 1H due to proton attached to nitrogen etc. The mass spectrum of compound **Ia**, the molecular ion peak at m/z = 330 corresponding to molecular formula $C_{16}H_{15}ClN_4O_2$.

All the synthesized compounds were screened for their antibacterial and antifungal activities. From the study of the biological activity data in reference to standard drug Gentamycin for antibacterial activity and Nystatin for antifungal activity (Table-2), we found that compound **Ic** and **IVg** showed good activity against *S. aureus* bacteria. Compounds **Ig** and **IVm** exhibited moderate activity against *S.aureus*. Compounds **Ih**, **IVc** and **IVh** showed moderate activity against *S. pyogenes*. The compound **Ib** and **Iva** exhibited good activity against *E. coli* bacteria. The compound **IVg** showed moderate activity against *E.coli* bacteria. Compound **Ib** showed good activity against *P. aeruginosa*. Compounds **Ik**, **IVc**, **IVg** and **IVo** showed low activity against *P. aeruginosa* bacteria. Most of the synthesized compounds failed to exhibit satisfactory antifungal activity against *C.albicans* fungi.



Scheme 1: Reaction schemefor the synthesis of compounds I (a-p)



Scheme 2: Reaction scheme for the synthesis of compounds Sr. No. IV (a-p)

Table 1. Physical properties of the synthesized compounds.

Sr. No.	Compound Id.	-R	Molecular Formula	Molecular Weight
1	Ia	4-Cl	$C_{16}H_{15}ClN_4O_2$	330.77
2	Ib	4-Br	$C_{16}H_{15}BrN_4O_2$	375.22
3	Ic	4-F	$C_{16}H_{15}FN_4O_2$	314.31
4	Id	4-NO_2	$C_{16}H_{15}N_5O_4$	341.32
5	Ie	3,4-di-OCH_3	$C_{18}H_{20}N_4O_4$	356.38
6	If	2,6-di-Cl	$C_{16}H_{14}C_{l2}N_4O_2$	365.21
7	Ig	3-Br	$C_{16}H_{15}BrN_4O_2$	375.22
8	Ih	2-NO_2	$C_{16}H_{15}N_5O_4$	341.32
9	Ii	3-NO_2	$C_{16}H_{15}N_5O_4$	341.32
10	Ij	2-Cl	$C_{16}H_{15}ClN_4O_2$	330.77
11	Ik	3-OH	$C_{16}H_{16}N_4O_3$	312.32
12	Il	4-OH	$C_{16}H_{16}N_4O_3$	312.32
13	Im	4-CN	$C_{17}H_{15}N_5O_2$	321.33
14	In	4-OCH_3	$C_{17}H_{18}N_4O_3$	326.35
15	Io	3-OCH_3	$C_{17}H_{18}N_4O_3$	326.35
16	Ip	4-CH_3	$C_{17}H_{18}N_4O_2$	310.35
17	IVa	4-Cl	$C_{25}H_{21}ClN_6O_2$	472.93
18	IVb	4-Br	$C_{25}H_{21}BrN_6O_2$	517.38
19	IVc	4-F	$C_{25}H_{21}FN_6O_2$	456.47
20	IVd	4-NO_2	$C_{25}H_{21}N_7O_4$	483.48
21	IVe	3, 4-OCH_3	$C_{27}H_{26}N_6O_4$	498.2
22	IVf	2,6-di-Cl	$C_{25}H_{20}Cl_2N_6O_2$	507.37
23	IVg	3-Br	$C_{25}H_{21}BrN_6O_2$	517.38
24	IVh	2-NO_2	$C_{25}H_{21}N_7O_4$	483.48
25	IVi	3-NO_2	$C_{25}H_{21}N_7O_4$	483.48
26	IVj	2-Cl	$C_{25}H_{21}ClN_6O_2$	472.93
27	IVk	3-OH	$C_{25}H_{22}N_6O_3$	454.18
28	IVl	4-OH	$C_{25}H_{22}N_6O_3$	454.18
29	IVm	4-CN	$C_{26}H_{21}N_7O_2$	463.49
30	IVn	4-OCH_3	$C_{26}H_{24}N_6O_3$	468.51
31	IVo	3-OCH_3	$C_{26}H_{24}N_6O_3$	468.51
32	IVp	4-CH_3	$C_{26}H_{24}N_6O_2$	452.51

Table 2.Biological activity in the terms of MIC of the synthesized compounds.

Sr. No.	Compound id	Minimum inhibitory concentration (MIC) (µ/ml)				Minimum inhibitory concentration(µ/ml)
		Gram positive bacteria		Gram negative bacteria		Fungus
		S.aureus MTCC-96	*S.pyogenes* MTCC-442	*E.coli* MTCC-443	*P.aeruginosa* MTCC-1688	*C.albicans* MTCC-227
1	Ia	250	500	250	250	250
	Ib	500	250	1000	**62.5**	250
2	Ic	**62.5**	500	500	250	500
3	Id	500	500	500	1000	500
4	Ie	500	1000	1000	500	1000
5	If	1000	500	500	500	1000
6	Ig	125	1000	250	250	250
7	Ih	250	125	1000	250	250
8	Ii	500	500	500	500	500
9	Ij	1000	500	500	500	1000
10	Ik	1000	500	250	125	250
11	Il	500	250	500	250	500
12	Im	250	1000	250	500	500
13	In	250	1000	1000	500	250
14	Io	500	500	500	250	1000
15	Ip	1000	500	500	1000	500
16	IVa	250	250	**62.5**	500	250
17	IVb	250	1000	500	250	500
18	IVc	125	125	1000	125	250
19	IVd	500	500	500	500	1000
20	IVe	500	1000	250	250	500
21	IVf	1000	500	1000	1000	250
22	IVg	**62.5**	500	125	125	1000
23	IVh	500	125	250	500	500
24	IVi	1000	500	1000	500	250
25	IVj	500	1000	500	1000	500
26	IVk	1000	500	500	250	1000
27	IVl	500	250	500	1000	250
28	IVm	125	500	500	500	250
29	IVn	250	500	250	500	250
30	IVo	1000	250	1000	125	500
31	IVp	500	1000	1000	250	1000
32	Gentamycin	0.25	0.50	0.05	1.0	-
	Nystatin	-	-	-	-	100

S.aureus=Staphyloccocusaureus, S.pyogenes=Streptococcus pyogenes, E. coli= Escherichiacoli, P.aeruginosa= Pseudomonas aeruginosa, C.albicans= Candida albicans. MIC= Minimal inhibitory concentration.

Conclusions:

From the present study it was observed that 1,2,4-triazole moiety can be considered as promising pharmacophore for better antibacterial activities. it was found that varying the substitution in the final structure affect the biological activities. Final compounds with halogen group like chloro, flouro and bromo were found to have good antibacterial activity. These final compounds failed to exhibit remarkable antifungal activity.

Acknowledgements:

The authors are thankful to Dr (Fr) Robert Arockiasamy, Principal, St. Xavier`s College (Autonomous) Ahmedabad for providing required research facilities.

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