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STUDIES ON SYNTHESIS OF SOME NOVEL FLUORINE CONTAINING TRIAZOLOPYRIMIDINE DERIVATIVES AND THEIR BIOLOGICAL EVALUATION

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ABSTARCT

An uncomplicated and well-organized method for the synthesis of triazolopyrimidine derivatives was achieved by the different acetoacetamides, 4-(5-fluoro-2-methoxypyrimidin-4-yloxy) benzaldehyde and 1H-1,2,4-triazol-5-amine refluxed with NN'-dimethyl formamide with high yield and no further purification required for compound. The structures of the products were supported by FTIR, ^{1}HMR and mass spectral data.

KEYWORDS : Acetoacetamide, 4-(5-fluoro-2-methoxypyrimidin-4-yloxy) benzaldehyde; 1H-1, 2, 4-triazol-5-amine, Antimicrobial activity.

INTRODUCTION

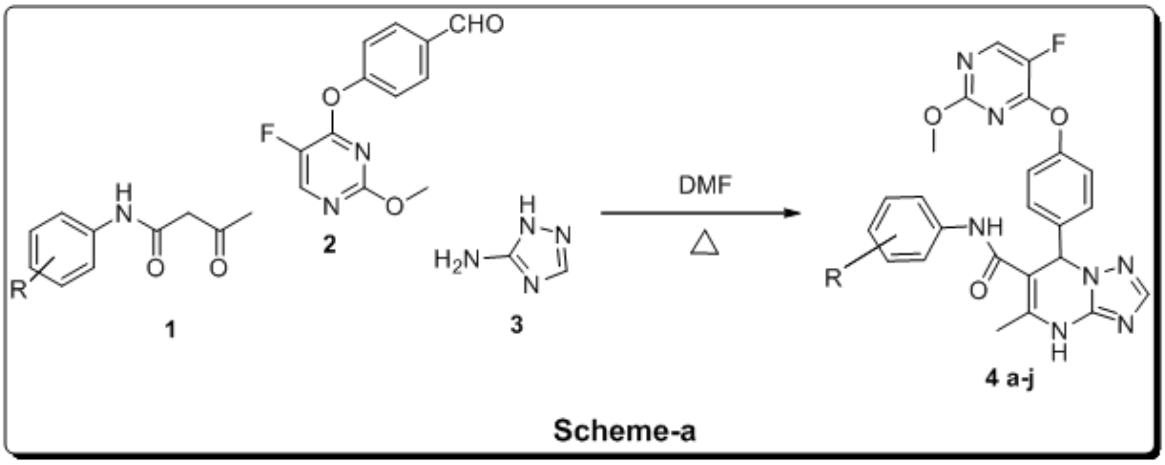
The Chemistry of pyrimidines & its derivatives have been studied for over a century due to their diverse biological activities such as antimicrobial, anticancer, antiHIV, antihypertensive, Cardiac

stimulant, antimalerial, antifungal, anticancer, antipyretic, analgesic, anti-inflammatory, potential herbicidal and leishmanicidal[1-17].

One of the most important factors in drug design is that **fluorine** is much more lipophilic than hydrogen; so incorporating fluorine atom in drug increases its lipophilicity, suppresses metabolic detoxification processes to increase the *in vivo* lifetime of drugs, improving partitioning into membranes and hence increasing bioavailability.

From the Standpoint of biological activity, fused heteroaromatic systems are often of much greater interest than the constituent monocyclic compounds. Recently, 1,2,4-triazolo[1,5-a]pyrimidines have aroused increasing attention from the chemical and biological viewpoints due to their diverse pharmalogical activities such as antitumor potency, inhibition of KDR kinase,antifungal effect and macrophage activation.Cevipabulin and its analogous represent a class of triazolo[1,5-a]pyrimidines and were proved to be potent anticancer agents with an unique mechanism of action in promoting tubulin polymerization. Revisions surveying the synthesis ,reactivity,spectroscopic characterization and crystallographic studies of 1,2,4-triazolo[1,5-c]pyrimidines[18] 1,2,4- triazolo[4,3-a]pyrimidines[19] and 1,2,4-triazolo[4,3-c]pyrimidines[20]

In a view of the all above facts we have synthesized some triazolopyrimidine derivatives containing an additional fluorinated pyrimidine ring in its framework to enhance its potency (Scheme-a).



Scheme-a

EXPERIMENTAL SECTION

Melting points were measured in open capillaries and are uncorrected. 1HNMR spectra were recorded on Brukur spectrophotometer (400MHz). Chemical shifts are expressed in units relative to TMS signal as internal reference. IR spectra were recorded on FT-IR Shimadzu-FT-IR 8400 spectrophotometer on KBr pallets. Mass spectra were recorded on GCMS QP2010 Gas Chromatograph. Thin Layer Chromatography was performed on silica gel-G using hexane:ethylacetate solvent system.

General Experimental procedure for the synthesis of triazolopyrimidines.

A mixture of different acetoacetamides (1mmol), 4-(5-fluoro-2-methoxypyrimidin-4-yloxy)benzaldehyde (1 mmol) and 1H-1, 2, 4-triazol-5-amine (2 mmol) swas refluxed in 0.5 ml of DMF for 30 min. After cooling, methanol (~15ml) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid triazolopyrimidine products, which were crystallized from ethanol.

7-(4-(5-fluoro-2-methoxypyrimidin-4-yloxy)phenyl)-N-(4-methylphenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4a)

Yield: 66%; mp 185ºC; Anal. Calcd. for $C_{25}H_{22}FN_7O_3$: C, 61.60; H, 4.55; F, 3.90; N, 20.11; O, 9.85; Found: C, 61.60; H, 4.52; F, 3.93; N, 20.16; O, 9.80 %; IR (cm-1): 3323 (N-H stretching of amide), 3100 (C-H stretching of aromatic ring), 2985 (C-H asymmetrical stretching of CH3 group), 2831 (C-H symmetrical stretching of CH3 group), 1656 (C=O stretching of amide), 1585, 1562 (C=O stretching of cyclic) 1510 (N-H deformation of pyrimidine ring), 1402 (C-H asymmetrical deformation of CH3 group), 1381 (C-H symmetrical deformation of CH3 group), 1290 (C-N-C stretching vibration of pyrimidine ring), 1269 (C-O-C asymmetrical stretching of OCH3), 1076 (C-F stretching), 775 (para-substituted), 725 (C-H in out plane deformation of aromatic ring); ^{1}H NMR (DMSO-d6) δ ppm: 2.22 (s, 3H, H), 2.18 (s, 3H, H), 3.67 (s, 3H, H), 6.58 (s, 1H, H), 7.02-7.04 (dd', 2H, H), 7.23-7.30 (dd', 4H, H), 7.38-7.40 (dd', 2H, H), 7.67 (s, 1H, H), 8.56 (s, 1H, H), 9.69 (s, 1H, H), 10.25 (s, 1H, H), MS: m/z 487.

7-(4-(5-fluoro-2-methoxypyrimidin-4-yloxy)phenyl)-N-(4-chlorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4b)

Yield: 69%; mp 190ºC; Anal. Calcd. for $C_{24}H_{19}ClFN_7O_3$: C, 56.75; H, 3.77; Cl, 6.98; F, 3.74; N, 19.30; O, 9.45; Found: C, 56.70; H, 3.79; Cl, 7.01; F, 3.75; N, 19.33; O, 9.41 %; IR (cm-1): 3273 (N-H stretching of amide), 3097 (C-H stretching of aromatic ring), 2974 (C-H asymmetrical stretching of CH3 group), 2864 (C-H symmetrical stretching of CH3 group), 1629 (C=O stretching of amide), 1583, 1510 (C=O stretching of cyclic) 1465 (N-H deformation of pyrimidine ring), 1431 (C-H asymmetrical deformation of CH3 group), 1375 (C-H symmetrical deformation of CH3 group), 1310 (C-N-C stretching vibration of pyrimidine ring), 1251 (C-O-C asymmetrical stretching of OCH3), 1047 (C-F stretching), 781 (para-substituted), 721 (C-H in out plane deformation of aromatic ring),MS: m/z 508.

7-(4-(5-fluoro-2-methoxypyrimidin-4-yloxy)phenyl)-N-(4-fluorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4c)

Yield: 59%; mp 171ºC; Anal. Calcd. for $C_{24}H_{19}F_2N_7O_3$: C, 58.65; H, 3.90; F, 7.73; N, 19.95; O, 9.77; Found: C, 58.68; H, 3.95; F, 7.79; N, 19.90; O, 9.70%; MS: m/z 491.

7-(4-(5-fluoro-2-methoxypyrimidin-4-yloxy)phenyl)-N-(4-bromophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4d)

Yield: 64; mp 181ºC; Anal. Calcd. for $C_{24}H_{19}BrFN_7O_3$: C, 52.19; H, 3.47; Br, 14.47; F, 3.44; N, 17.75; O, 8.69; Found: C, 52.22; H, 3.45; Br, 14.48; F, 3.43; N, 17.77; O, 8.66%; MS: m/z 552.

7-(4-(5-fluoro-2-methoxypyrimidin-4-yloxy)phenyl)-N-(4-methoxyphenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4e)

Yield: 57; mp 173ºC; Anal. Calcd. for $C_{25}H_{22}FN_7O_4$: C, 59.64; H, 4.40; F, 3.77; N, 19.47; O, 12.71; Found C, 59.59; H, 4.45; F, 3.80; N, 19.45; O, 12.70%; MS: m/z 503.

7-(4-(5-fluoro-2-methoxypyrimidin-4-yloxy)phenyl)-N-(3-chlorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4f)

Yield: 71%; mp 188ºC; Anal. Calcd. for $C_{24}H_{19}ClFN_7O_3$: C, 56.75; H, 3.77; Cl, 6.98; F, 3.74; N, 19.30; O, 9.45; Found: C, 56.69; H, 3.75; Cl, 7.02; F, 3.79; N, 19.30; O, 9.44 %; MS: m/z 508.

7-(4-(5-fluoro-2-methoxypyrimidin-4-yloxy)phenyl)-N-(3-fluorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4g)

Yield: 57%; mp 168ºC; Anal. Calcd. for $C_{24}H_{19}F_2N_7O_3$: C, 58.65; H, 3.90; F, 7.73; N, 19.95; O, 9.77; Found: C, 58.69; H, 3.93; F, 7.70; N, 19.93; O, 9.77%; MS: m/z 491.

7-(4-(5-fluoro-2-methoxypyrimidin-4-yloxy)phenyl)-N-(3-bromophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4h)

Yield: 66%; mp 179ºC; Anal. Calcd. for $C_{24}H_{19}BrFN_7O_3$: C, 52.19; H, 3.47; Br, 14.47; F, 3.44; N, 17.75; O, 8.69; Found: C, 52.20; H, 3.40; Br, 14.49; F, 3.47; N, 17.78; O, 8.67%; MS: m/z 552

7-(4-(5-fluoro-2-methoxypyrimidin-4-yloxy)phenyl)-N-(2-chlorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4i)

Yield: 71%; mp 188ºC; Anal. Calcd. for $C_{24}H_{19}ClFN_7O_3$: C, 56.75; H, 3.77; Cl, 6.98; F, 3.74; N, 19.30; O, 9.45; Found: C, 56.74; H, 3.70; Cl, 7.07; F, 3.74; N, 19.32; O, 9.42 %; MS: m/z 508.

7-(4-(5-fluoro-2-methoxypyrimidin-4-yloxy)phenyl)-N-(2-bromophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4j)

Yield: 63%; mp 171ºC; Anal. Calcd. for $C_{24}H_{19}BrFN_7O_3$: C, 52.19; H, 3.47; Br, 14.47; F, 3.44; N, 17.75; O, 8.69; Found: C, 52.22; H, 3.41; Br, 14.55; F, 3.50; N, 17.75; O, 8.60%; MS: m/z 552.

ANTIMICROBIAL EVALUATION

Total of the Prepared compounds **(4a-j)** were experienced for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria **Staphylococcus aureus** MTCC-96, **Streptococcus pyogenes** MTCC 443, two Gram-negative bacteria **Escherichia coli** MTCC 442, **Pseudomonas aeruginosa** MTCC 441 and three fungal strains **Candida albicans** MTCC 227, **Aspergillus Niger** MTCC 282, **Aspergillus clavatus** MTCC 1323 taking **gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin** as regular drugs.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, definited as the lowly concentration of the compound preventing the observable growth, were determined by using micro dilution broth method according to NCCLS standards [30].

Minimal Inhibition Concentration [MIC]

The main advantage of the 'Broth Dilution Method' for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

- Serial dilutions were prepared in primary and minor screening.
- The control tube containing no antibiotic is immediately subcultured by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 ^{0}C overnight.
- The MIC of the control organism is read to check the accuracy of the drug concentrations.
- The lowest concentration inhibiting growth of the organism is recorded as the MIC.
- The amount of growth from the control tube before incubation (which represents the original inoculums) is compared.

In vitro Antimicrobial Screening Results for (4a-j)

Code	**Minimal inhibition concentration (µg mL^{-1})**						
	Gram-positive		**Gram-negative**		**Fungal species**		
	S.a.	***S. p.***	***E.c.***	***P.a.***	***C. a.***	***A. n.***	***A.c.***
4a	450	350	450	450	250	350	350
4b	450	300	250	300	350	450	300
4c	100	350	500	350	350	450	450
4d	300	400	400	350	350	400	500
4e	350	350	100	450	350	350	100
4f	400	450	150	450	250	500	350
4g	350	350	320	450	300	300	150
4h	300	350	350	200	350	350	350
4i	350	400	450	500	400	350	200
4j	400	300	300	450	350	250	500
Gentamycin	0.25	0.5	0.05	1	-	-	-
Ampicillin	245	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-

CONCLUSION

In tallness, we include synthesized of novel 1,2,4-triazolo[1,5-a]pyrimidine derivatives using easy and proper method. This method produces these products in supreme yields and difficulty-free workup. The isolated products are unadulterated and no need of purification.

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