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SYNTHESIS, CHARCTERISATION AND BIOLOGICAL EVOLUTION OF 7-(4-(4-(TRIFLUOROMETHYL)-2-NITROPHENOXY)PHENYL)-N-(SUBSTITUTEDPHENYL)-4,7-DIHYDRO-5-METHYL-[1,2,4]TRIAZOLO[1,5-A]PYRIMIDINE-6-CARBOXAMIDE

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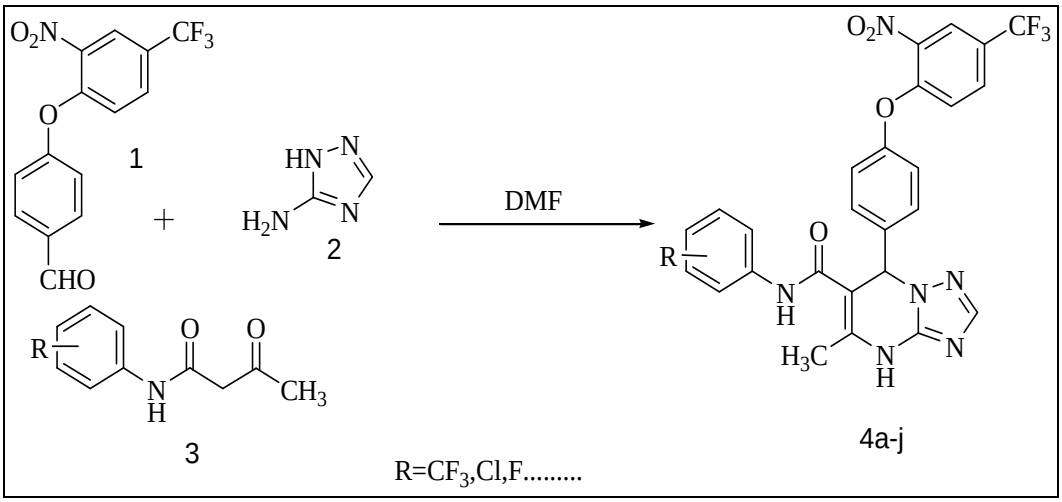
ABSTRACT
A uncomplicated and well-organized method for synthesis of fluoropyrimidine derivatives was achieved from N-(substitutedphenyl)-3-oxobutanamide, 4-(4-(trifluoromethyl)-2-nitrophenoxy)benzaldehyde and 2H-1,2,4-triazol-3-amine refluxed with N N'-dimehyl formamide with good yield and no further purification requirement for compound . The structures of the products were supported by FTIR, ^{1}HMR and mass spectral data and microbiological activity completed of all compounds.

KEYWORDS: N-(substitutedphenyl)-3-oxobutanamide, 4-(4-(trifluoromethyl)-2-nitrophenoxy)benzaldehyde, 2H-1,2,4-triazol-3-amine only refluxed.

INTRODUCTION

At that time pyrimidine derivatives most important research in the world like that of triazolopyrimidine is very imperative work of pyrimidine derivatives part because its biological activity like that antimicrobial, anti cancer, anti HIV, antihypertensive, cardiac stimulant, antimalarial, antifungal, anti-HBV, antimicrobial, anticancer, antipyretic, analgesic, antiinflammatory, potential herbicidal, and leishmanicidal activities.[1-17] And here new heterocyclic compounds and novel methods for their synthesis is a major topic in contemporary medicinal chemistry.[18-21] Cevipabulin and its analogs 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.

we have developed a new modesty for the synthesis 7-(4-(4-(trifluoromethyl)-2-nitrophenoxy)phenyl)-n-(substitutedphenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide ***(4a-j)*** with the advantage of fine yield and environmentally lenience.



METHOD AND MATERIAL

A mixture of the 2H-1,2,4-triazol-3-amine, N-(substitutedphenyl)-3-oxobutanamide and 4-(4-(trifluoromethyl)-2-nitrophenoxy) benzaldehyde was refluxed in DMF for 30 min. After cooling, methanol was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid products which were recrystallized from ethanol.

RESULTS AND DISCUSSION

7-(4-(4-(trifluoromethyl)-2-nitrophenoxy)phenyl)-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4a)

Yield: 63%; mp 172ºC; Anal. Calcd. for $C_{27}H_{18}F_6N_6O_4$: C, 53.65; H, 3.00; F, 18.86; N, 13.90; O, 10.59; Found: C, 53.65; H, 3.02; F, 18.88; N, 13.95; O, 10.50%; IR (cm-1): 3114 (N-H stretching of amide), 3009 (C-H stretching of aromatic ring), 2956 (C-H asymmetrical stretching of CH3 group), 2902 (C-H symmetrical stretching of CH3 group), 1657 (C=O stretching of amide), 1576, 1518 (C=O stretching of cyclic) 1515 (N-H deformation of pyrimidine ring), 1460 (C-H asymmetrical deformation of CH3 group), 1345 (C-H symmetrical deformation of CH3 group), 1305 (C-N-C stretching vibration of pyrimidine ring), 1257 (C-O-C asymmetrical stretching of OCH3), 1029 (C-F stretching), 820 (para-substituted), 708 (C-H in out plane deformation of aromatic ring); ^{1}H NMR (DMSO-d6) δ ppm: 1.35-1.37 (s, 3H, H), 5.34 (s, 1H, H), 7.54-7.64 (dd', 4H, H), 7.92-7.93 (dd', 4H, H), 8.09-8.13 (d, 2H, H), 8.33(s, 2H, H), 8.61 (s, 1H, H), 8.93 (s, 1H, H),: m/z 604.

7-(4-(3-(trifluoromethyl)-2-nitrophenoxy)phenyl)-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4b)

Yield: 60%; mp 174ºC; Anal. Calcd. for $C_{27}H_{18}F_6N_6O_4$: C, 53.65; H, 3.00; F, 18.86; N, 13.90; O, 10.59; Found: C, 53.66; H, 3.01; F, 18.88; N, 13.90; O, 10.55%; MS: m/z 604.

7-(4-(2-(trifluoromethyl)-2-nitrophenoxy)phenyl)-N-(4-(trifluoromethyl)phenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4c)

Yield: 54%; mp 177ºC; Anal. Calcd. for $C_{27}H_{18}F_6N_6O_4$: C, 53.65; H, 3.00; F, 18.86; N, 13.90; O, 10.59; Found: C, 53.65; H, 3.01; F, 18.85; N, 13.91; O, 10.58%; MS: m/z 604.

7-(4-(4-(trifluoromethyl)-2-nitrophenoxy)phenyl)-N-(4-chloro-3-(trifluoromethyl)phenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4d)

Yield: 63; mp 171ºC; Anal. Calcd. for $C_{27}H_{17}ClF_6N_6O_4$: C, 50.76; H, 2.68; Cl, 5.55; F, 17.84; N, 13.15; O, 10.02; Found: C, 50.80; H, 2.69; Cl, 5.50; F, 17.83; N, 13.13; O, 10.05 %; MS: m/z 639.

7-(4-(4-(trifluoromethyl)-2-nitrophenoxy)phenyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4e)

Yield: 55; mp 180ºC; Anal. Calcd. for $C_{27}H_{17}F_7N_6O_4$: C, 52.10; H, 2.75; F, 21.37; N, 13.50; O, 10.28; Found C, 52.11; H, 2.76; F, 21.39; N, 13.54; O, 10.20%; MS: m/z 622.

7-(4-(4-(trifluoromethyl)-2-nitrophenoxy)phenyl)-N-(2-chloro-4-(trifluoromethyl)phenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4f)

Yield: 61%; mp 191ºC; Anal. Calcd. for $C_{27}H_{17}ClF_6N_6O_4$: C, 50.76; H, 2.68; Cl, 5.55; F, 17.84; N, 13.15; O, 10.02; Found: C, 50.77; H, 2.69; Cl, 5.58; F, 17.86; N, 13.10; O, 10.00 %; MS: m/z 639.

7-(4-(4-(trifluoromethyl)-2-nitrophenoxy)phenyl)-4,7-dihydro-5-methyl-N-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4g)

Yield:60%; mp 187ºC; Anal. Calcd. for $C_{27}H_{18}F_6N_6O_5$: C, 52.27; H, 2.92; F, 18.37; N, 13.54; O, 12.89; Found: C, 52.26; H, 2.93; F, 18.36; N, 13.57; O, 12.87 %; MS: m/z 620.

7-(4-(4-(trifluoromethyl)-2-nitrophenoxy)phenyl)-4,7-dihydro-5-methyl-N-(3-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4h)

Yield: 67%; mp 197ºC; Anal. Calcd. for $C_{27}H_{18}F_6N_6O_5$: C, 52.27; H, 2.92; F, 18.37; N, 13.54; O, 12.89; Found: C, 52.28; H, 2.93; F, 18.38; N, 13.56; O, 12.84 %; MS: m/z 620.

7-(4-(4-(trifluoromethyl)-2-nitrophenoxy)phenyl)-4,7-dihydro-5-methyl-N-(2-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4i)

Yield: 67%; mp 176ºC; Anal. Calcd. for $C_{27}H_{18}F_6N_6O_5$: C, 52.27; H, 2.92; F, 18.37; N, 13.54; O, 12.89; Found: C, 52.28; H, 2.93; F, 18.35; N, 13.56; O, 12.87 %; MS: m/z 620.

N-(3,5-bis(trifluoromethyl)phenyl)-7-(4-(4-(trifluoromethyl)-2-nitrophenoxy)phenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4j)

Yield: 64%; mp 177ºC; Anal. Calcd. for $C_{28}H_{17}F_9N_6O_4$: C, 50.01; H, 2.55; F, 25.43; N, 12.50; O, 9.52; Found: C, 50.00; H, 2.54; F, 25.44; N, 12.53; O, 9.50 %; MS: m/z 672.

BIOLOGICAL EVALUATION

Antimicrobial evaluation

Total of the Prepared compounds 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, chloramphenicol, norfloxacin, nystatin and greseofulvin* as regular drugs.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, specified as the humble concentration of the compound preventing the observable growth, were determined by using micro dilution broth method according to NCCLS(National Committee for Clinical Laboratory Standards) standards.

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 secondary screening.
- The control tube containing no antibiotic is immediately subcultured (before inoculation) 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 35 ^{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.

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	250	500	450	400	650	250	500
4b	100	250	250	300	600	400	500
4c	250	320	450	500	600	350	250
4d	320	500	400	200	650	500	450
4e	500	350	500	400	500	350	450
4f	450	250	350	400	650	400	250
4g	500	500	350	400	550	350	550
4h	350	350	350	500	650	450	250
4i	250	450	150	250	650	250	450
4j	100	250	450	550	600	250	350
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Griseofulvin	-	-	-	-	450	100	100

CONCLUSION

In loftiness, we include synthesized of narrative pyrimidine derivatives using trouble-free and appropriate method. This method produces these products in supreme yields and difficulty-free workup. The isolated products are unadulterated and not requirement purification.

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