International Research Journal of Natural and Applied Sciences
ISSN: (2349-4077)
Impact Factor- 5.46, Volume 4, Issue 7, July 2017
Website- www.aarf.asia, **Email** : editor@aarf.asia , editoraarf@gmail.com

STUDIES ON SYNTHESIS OF SOME NOVEL FLUORINATED PYRIMIDINE TRIONE DERIVATIVES

Sanket Y. Mavawala[1] , Kiran S. Nimavat[2] , Kartik B. Vyas[3]

[1]Department of Chemistry, Pacific Academy of Higher Education & Research University, Udaipur, Rajsthan (India)

[2]Department of Chemistry, Government Science College, Ghandhinagar, Gujarat (India)

[3]Department of Chemistry, Sheth L.H.College, Mansa, Ghandhinagar, Gujarat (India)

ABSTRACT

The synthesis of various pyrimidine triones derivatives were carried out by reaction of 4-fluoroaniline with phenylchloroformate to give phenylcarbamates which on condensation with various fluorinated anilines to give substituted urea derivatives. Urea derivatives were treated with malonic acid following by the treatment with various aldehydes and meldrumacid to produce final products.

KEYWORDS: Pyrimidine triones, 4-fluoroaniline, Phenylchloroformate, Phenylcarbamates, Substituted urea derivatives

INTRODUCTION

It is no great surprise that around a fifth of all drugs on the market today contain at least one **Fluorine** substituent. The inclusion of a **fluorine atom** in a drug molecule can influence not only pharmacokinetic properties, such as absorption, tissue distribution, secretion, and the route and rate of biotransformation but also its pharmacodynamics and toxicology. Introducing **F & CF_3** substituent often improves lipophilicity, and suppresses metabolic detoxification processes to increase the *in vivo* lifetime of drugs.

The Chemistry of pyrimidines & its derivatives have been studied for over a century due to their diverse biological activities such as antimicrobial, anticancer, anti HIV, antihypertensive, Cardiac stimulant, antimalerial, antifungal, anticancer, antipyretic, analgesic, anti-inflammatory, potential herbicidal and leishmanicidal1[-17].

In a view of the all above facts we have synthesized some novel Pyrimidine triones derivatives containing fluorine atom in its framework.

1. OBJECTIVES OF PRESENT WORK

1. To synthesize substituted urea derivatives **3a-c by** condensation reaction between 4-fluoroaniline and phenylchloroformate to produce phenylcarbamates followed by condensation with various fluorinated anilines.

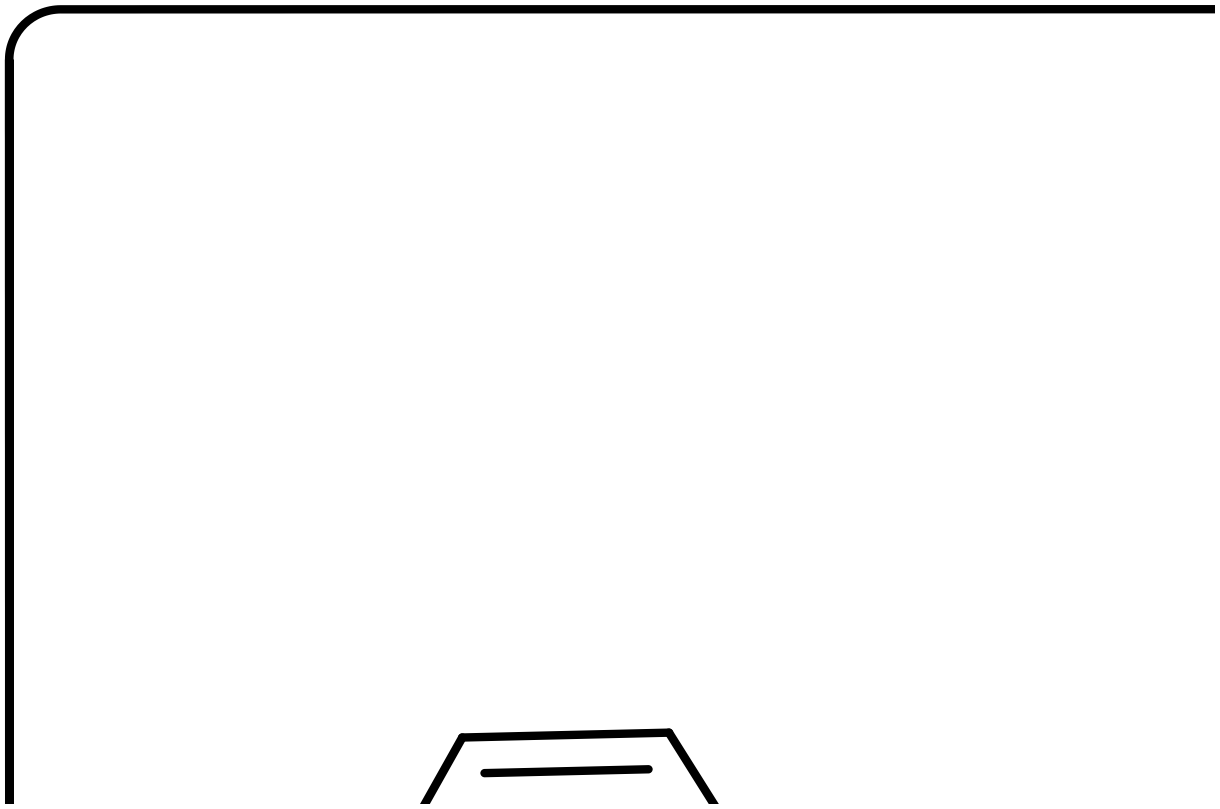
2. To find out new synthetic pathway for condensation reactions of aromatic aldehydes,meldrumacid and substituted pyrimidines to affords various condensation products **A1-A16**.

3. To check the scope of the novel protocol for synthesizing a good library of pyrimidine type heterocyclic derivatives.

4. To characterize all the synthesized compounds by ^{1}H NMR, ^{13}C NMR, IR, MASS spectroscopic techniques.

2.1 SCHEME

The synthesis of various pyrimidine triones **A1-A16** were carried out by reaction of 4-fluoroaniline **1** with phenylchloroformate to give phenylcarbamates which on condensation with various fluorinated anilines **2a-c** to give substituted urea derivatives **3a-c.** Compounds **3a-c** were treated with malonic acid to produced compounds **4a-c** which on treatment with various aldehydes **5a-d** and meldrumacid to produced final products **A1-A16** (**Scheme 3I**).



2.2 Characteristics data showing the synthesis compounds A1-A16.

From the **Table 2.3** show the various condensation products **A1-A16** of condensation reaction between **various aldehydes and Fluorosubstituted anilines.** It clearly indicates that the compounds bearing electron withdrawing group are synthesized in shorter reaction time as compared to compounds bearing electron donating group. Compounds **A4, A8, A12 & A16** bearing electron withdrawing were synthesized in 6 hr. as shorter time as compared to compound **A1, A5, A9 and A13** bearing electron donating group in 8 hr.

Table:2.3 : Characteristic data showing synthesis of compounds A1-A16 from various aldehydes and Fluorosubstituted anilines.

Sr. No.	Compounds Code	R'	R_1	R_2	R_3	Reaction Time[a] (hr.)	% Yiled[b]
1	A1	4-OCH_3	F	H	H	8	70
2	A2	4-CH_3	F	H	H	7.5	75
3	A3	4-Cl	F	H	H	6.5	78
4	A4	2-NO_2	F	H	H	6.0	85
5	A5	4-OCH_3	H	F	H	8	70
6	A6	4-CH_3	H	F	H	7.5	75
7	A7	4-Cl	H	F	H	6.5	78
8	A8	2-NO_2	H	F	H	6.0	85
9	A9	4-OCH_3	F	F	H	8	70
10	A10	4-CH_3	F	F	H	7.5	75
11	A11	4-Cl	F	F	H	6.5	78
12	A12	2-NO_2	F	F	H	6.0	85
13	A13	4-OCH_3	F	F	F	8	70
14	A14	4-CH_3	F	F	F	7.5	75
15	A15	4-Cl	F	F	F	6.5	78
16	A16	2-NO_2	F	F	F	6.0	85

[a]Reaction is monitored by TLC.

[b]Isolated yield

All the compounds were crystallized from hot ethanol and percentage yield was calculated after crystallization step. All the synthesized compounds have been characterized by melting point, ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopy. All the data were in agreement with the cited literature.

3.EXPERIMENTAL

Melting points were determined using µThermoCal$_{10}$ (Analab scientific Pvt. Ltd.) melting point apparatus and are uncorrected. TLC was carried out using aluminum sheets precoated with silica gel 60 F_{254}.

3.1 Chemicals and Reagents

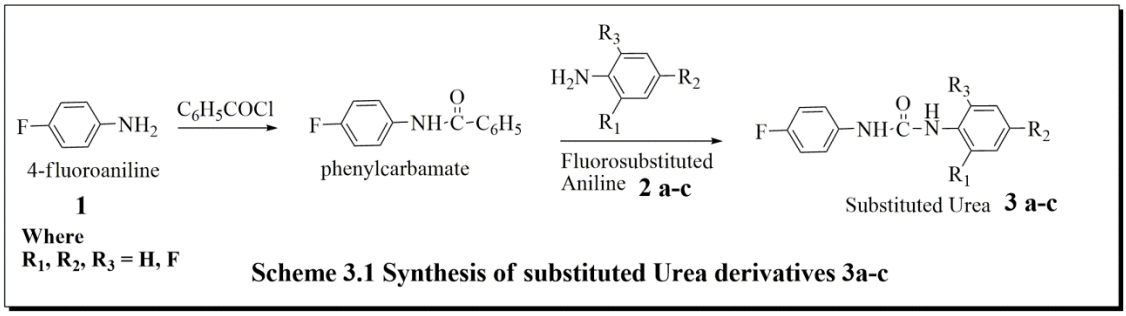
All chemicals used were of laboratory reagent grade and used without further purification**.** Phenylchloroformate (PCF), triethylamine, Acetonitrile, Malonic acid 4-

fluoroaniline, various aldehydes, meldrum acid, piperidine were used as received from Merck, Mumbai, India. All the solvent were used as received from Merck, Mumbai, India.

3.2 Synthesis

3.2.1 Synthesis of Substituted Urea derivatives 3a-c.

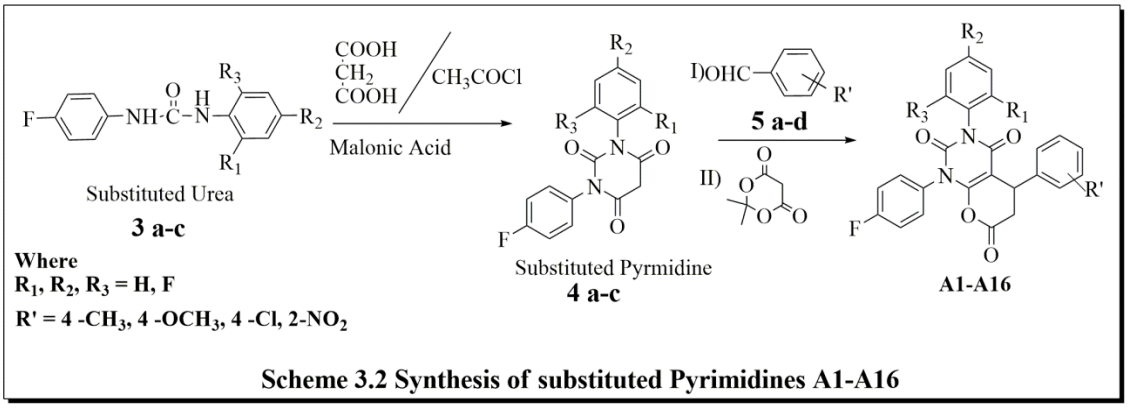
In a 250 ml round bottom flask, Phenyl chloroformate (PCF) (1.1 mol) was added drop wise at 10-15 °C to the well stirred solution of 4-fluoroaniline **1** (0.01mol), triethylamine (0.02mol) in Acetonitrile (20ml).Reaction was then maintained at 25-28 °C for 30 min. Check TLC in 70:30 (Hexane: Ethylacetate) to ensure no un reacted 4-fluoroaniline. To this reaction mass, add fluorosubstituted aniline **(2a-c)** followed by drop wise addition of Methanesulfonic acid at 35 °C within time period of 30 min. Reaction was then maintained at 25-28 °C for 80 min. Completion of reaction was checked by TLC in 60:40 (Hexane: Ethylacetate).The formed precipitates was filtered out & filter ml was concentrated. Concentrated mass was slowly added to the cooled MeOH under stirring to get shiny white crystals of substituted urea **(3a-c)** which was filtered out & dried (**Scheme 3.1)**.



Scheme 3.1 Synthesis of substituted Urea derivatives 3a-c

3.2.2 Synthesis of various Pyrimidines A1-A16.

In a 250 ml round bottom flask, **3a-c** (0.01mol) was heated with Malonic acid (0.0115 mol) and acetyl chloride (20 ml) under reflux temperature for 3-4 hr. Cooled mass was then poured into crushed ice under vigorous stirring & stirred for 30 min. The formed precipitates was filtered out, washed & crystallized by MeOH to give **4a-c.** A mixture of **4a-c** (0.01 mol), various aldehydes **5a-d** (0.01 mol), meldrum acid (0.01mol) and catalytic amount of piperidine in 20 ml ethanol was refluxed for 2-3 hr. The reaction mass was cooled to room temperature, separated solid was filtered out and recrystallized by ethanol to give **A1-A16 (Scheme 3.2)**.

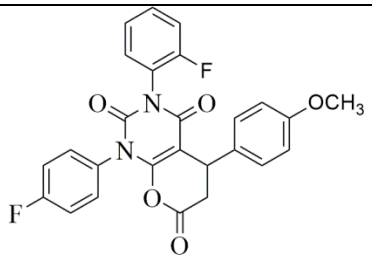


Scheme 3.2 Synthesis of substituted Pyrimidines A1-A16

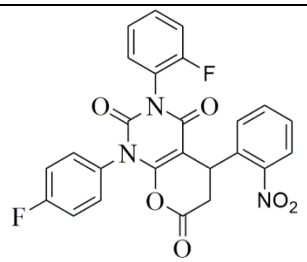
4. CHARACTERIZATION OF COMPOUNDS A1-A16

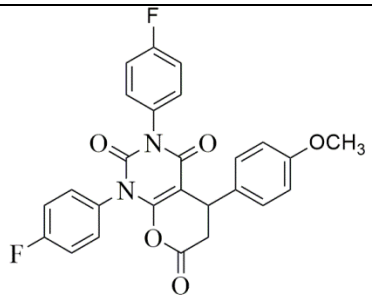
Melting points were determined using µThermoCal$_{10}$ (Analab scientific Pvt. Ltd.) melting point apparatus and are uncorrected. TLC was carried out using aluminum sheets precoated with silica gel 60 F_{254} (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrophotometer operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR, as solutions in DMSO-*d*$_6$. Chemical shifts (δ) are expressed in ppm and referenced to the residual protic solvent. FT-IR spectra were recorded on Shimadzu FT-IR 8401 spectrophotometer using KBr disc, and are expressed in wave numbers (cm^{-1}). The mass spectra (LCMS) were recorded on Shimadzu LCMS-2010 spectrometer.

4.1 Spectral data analysis of selected compounds

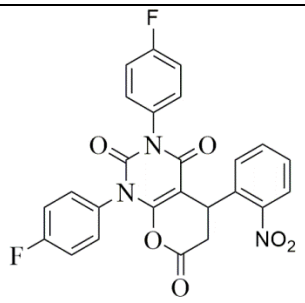
Compound code: A1	
Molecular formula: $C_{26}H_{18}F_2N_2O_5$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, d), 3.6 (3H, s), 4.2 (1H, t), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz,	32.5, 39.6, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9,

$CDCl_3$) δ ppm:	143.6, 151.8, 153.6, 155.1, 155.8. 158, 162, 170
IR cm^{-1} (KBr):	3251, 1750, 1710, 1644, 1614, 1592, 1560, 752.
Mass (M+1):	476.0
Elemental analysis:	**Calculated (%):** C: 65.55; H: 3.81; N:5.88 **Found (%) :** C:65.60; H: 3.86; N:5.86

Compound code: A4	
Molecular formula: $C_{25}H_{15}F_2N_3O_6$	
M. P. (°C): >250	
^1H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, d), 4.2 (1H, t), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.6, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 157.8. 158, 162, 170
IR cm^{-1} (KBr):	3032, 1750, 1710, 1644, 1614, 1592, 1569, 744.
Mass (M+1):	491.0
Elemental analysis:	**Calculated (%):** C: 61.10; H: 3.08; N: 8.55 **Found (%) :** C: 61.86; H: 3.54; N:8.18

Compound code: A5	
Molecular formula: $C_{26}H_{18}F_2N_2O_5$	
M. P. (°C): >250	

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, d), 3.6 (3H, s), 4.2 (1H, t), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.6, 60.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 157.8. 158, 162, 170
IR cm^{-1} (KBr):	3031, 1750, 1710, 1644, 1614, 1592, 1569, 750.
Mass (M+1):	476.0
Elemental analysis:	**Calculated (%):** C: 65.55; H: 3.81; N:5.88 **Found (%) :** C:65.60; H: 3.86; N:5.86

Compound code: A8	
Molecular formula: $C_{25}H_{15}F_2N_3O_6$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, d), 4.2 (1H, t), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.6, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 156.8. 158, 162, 170
IR cm^{-1} (KBr):	2800, 1750, 1710, 1644, 1614, 1592, 1569, 745.
Mass (M+1):	491.0
Elemental analysis:	**Calculated (%):** C: 61.10; H: 3.08; N: 8.55 **Found (%) :** C: 61.86; H: 3.54; N:8.18

CONCLUSION

In tallness, we include synthesized of novel fluorinated pyrimidine triones derivatives using easy and proper method. This method produces these products in supreme yields and difficulty-free workup.

ACKNOWLEDGMENT

Author is thankful to Head, R&D Center, FMC-Cheminova India Limited (Panoli, Gujarat) for providing laboratory facility to carry out this research work.

REFERENCES

1. Allen J.G., Bourbeau M.P., Wohlhieter G.E., Bartberger M.D., Michelsen K., Hungate R., Gadwood R.C. et al.: J. Med. Chem. 52, 7044 (2009).
2. Tang W., Shi D.Q.: J. Heterocycl. Chem., 47, 162 (2010).
3. Chen Q., Liu Z.M., Chen C.N., Jiang L.L., Yang G.F.: Chem. Biodivers. 6, 1254 (2009).
4. El-Koussi N.A., Omar F.A., Abdel-Aziz S.A., Radwan M.F.: Bull. Pharm. Sci. 27, 141 (2004).
5. Lakomska I., Wojtczak A., Sitkowski J., Kozerski L., Szlyk E.: Polyhedron 27, 2765 (2008).
6. Lakomska I.: Inorg. Chim. Acta 362, 669 (2009)
7. R. Trivedi, B. H. Dholariya, C. P. Vakhariya, D. K. Dodiya, H. K. Ram, V. B. Kataria, A. B. Siddiqui & V. H. Shah; Medicinal Chemistry Research, 2011; 19(7): 617-716.
8. K. Ahir, H. Ram, D. Dodiya and V. Shah; Journal of Chemical and Pharmaceutical Research, 2013; 5(6): 113-116.
9. R. S. Pada, R. N. Nandaniya, H. K. Ram and V. H. Shah; Journal of Chemical and Pharmaceutical Research, 2012; 4(7): 3557-3561.
10. Borisagar M, Baldev A, Nimavat K, Ram H, Vyas K.; International Journal for Pharmaceutical Research Scholars, 2012; 1: I-3.
11. Patel KN, Joshi KA, Ram HK, International Journal for Pharmaceutical Research Scholars (IJPRS), 2015; 4: 210-214.

12. Vora JH, Joshi KA, Ram HK, International Journal for Pharmaceutical Research Scholars (IJPRS), 2015; 4: 163-167.
13. Fischer G.: Adv. Heterocycl. Chem. 95, 143 (2008).
14 .Gujjar R., Marwaha A., El Mazouni F., White J., White K.L., Creason S., Shackleford D. et al.: J. Med. Chem. 52, 1864 (2009).
15. Chen Q., Zhu X.L., Jiang L.L., Liu Z.M., Yang G.F.: Eur. J. Med. Chem. 43, 595 (2008).
16. Yu W., Goddard C., Clearfield E., Mills C., Xiao T., Guo H., Morrey J.D. et al.: J. Med. Chem. 54, 5660 (2011).
17. El-Gendy M.M.A., Shaaban M., Shaaban K.A., El-Bondkly A.M., Laatsch H.: J. Antibiot. 61, 149 (2008).