Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Multicomponent synthesis and anticancer activity studies of novel 6-(Trifluoromethyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate derivatives

Anil Valeru, Zhi-Bin Luo, Imran Khan, Bin Liu, Bhavanarushi Sngepu, Narender Reddy Godumagadda, Yin Xu & Jimin Xie

To cite this article: Anil Valeru, Zhi-Bin Luo, Imran Khan, Bin Liu, Bhavanarushi Sngepu, Narender Reddy Godumagadda, Yin Xu & Jimin Xie (2018): Multicomponent synthesis and anticancer activity studies of novel 6-(Trifluoromethyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate derivatives, Synthetic Communications, DOI: 10.1080/00397911.2018.1490769

To link to this article: https://doi.org/10.1080/00397911.2018.1490769

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2018.1490769

Taylor & Francis
Taylor & Francis Group

Multicomponent synthesis and anticancer activity studies of novel 6-(Trifluoromethyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate derivatives

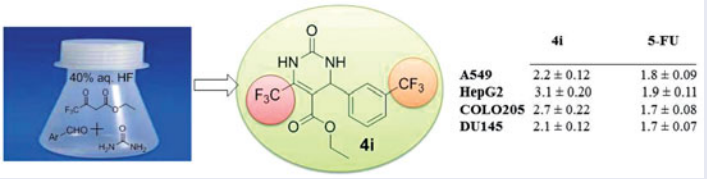
Anil Valeru[a], Zhi-Bin Luo[a], Imran Khan[a], Bin Liu[a], Bhavanarushi Sngepu[a], Narender Reddy Godumagadda[b], Yin Xu[a] and Jimin Xie[a]

[a]School of Chemistry and Chemical Engineering, Jiangsu University, Zhenjiang, P.R.China; [b]Medicinal Chemistry and Pharmacology Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, India

ABSTRACT

A series of novel 6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives were obtained in good yields from ethyl 4,4,4-trifluoro-3-oxobutanoate, urea, and aryl aldehyde via Biginelli multicomponent reaction. All the corresponding products **4a–4p** were examined against four human cancer cell lines (A549, HepG2, COLO205 and DU145) and compounds **4e**, **4i**, and **4 m** which showed promising anticancer activity have been identified.

GRAPHICAL ABSTRACT



	4i	5-FU
A549	2.2 ± 0.12	1.8 ± 0.09
HepG2	3.1 ± 0.20	1.9 ± 0.11
COLO205	2.7 ± 0.22	1.7 ± 0.08
DU145	2.1 ± 0.12	1.7 ± 0.07

ARTICLE HISTORY
Received 15 April 2018

KEYWORDS
6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate; anticancer activity; Biginelli condensationIntroduction

Multicomponent reactions (MCRs)[1] are proved effective protocols to build complex molecules in a single step. Dihydropyrimidinones (DHPMs) are key building blocks in N-containing heterocyclic compounds and play an important role in synthetic and medicinal chemistry wherein exhibit wide range of applications such as antiviral,[2] anticancer,[3] antibacterial and antifungal,[4] and calcium channel modulation.[5] 5-Fluoro Uracil which has pyrimidine dione shows anticancer activity. Monastrol(I), with the pyrimidine-2-thione motif, specifically inhibits the motility of the mitotic kinesin Eg5,[6] meanwhile SQ 32926 (II),[7] and Mon-97 (III)[8] display antihypertensive and anticancer activities (Fig. 1).

Biginelli[9–14] condensation is a simple, well-known, atom-economical, and direct method for the construction of DHPMs by the three-component reaction of aldehyde, 1,3-dicarbonyl compound, and urea under acidic conditions. The available

CONTACT Jimin Xie xiejm@ujs.edu.cn; Zhibin Luo luozb@ujs.edu.cn School of Chemistry and Chemical Engineering, Jiangsu University, Zhenjiang, 212013, China.

Supplemental data for this article can be accessed on the publisher's website.

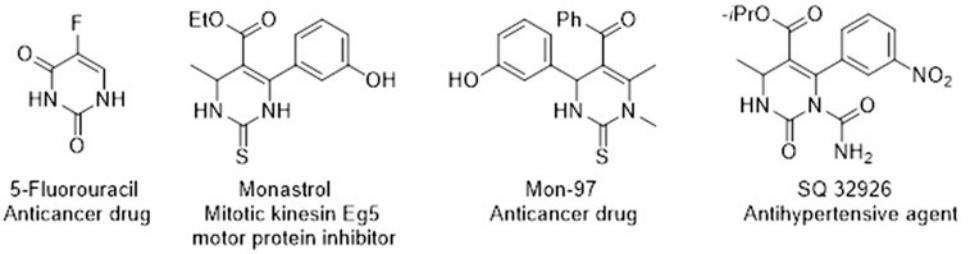


Figure 1. Biological activity compounds based on Dihydropyrimidinones (DHPMs).

methodologies for the Biginelli reaction in the literature employs catalysts such as Fe_3O_4 SBA-15(mesoporous nanocatalyst),[15] [Gmim]Cl-Cu(II) complex,[16] Mg/Ca–Al–CO_3 hydrotalcite,[17] phosphoric acid,[18] poly(1-vinyl-3-(3-sulfopropyl) imidazolium hydrogen sulfate) (poly(SIL)),[19] chiral organocatalyst,[20] ionic liquid ([Hmim]HSO_4/TMSCl),[21] perchloric acid doped silica ($HClO_4/SiO_2$),[22] bioglycerol-based sulfonic acid functionalized carbon catalyst,[23] and t-BuOK,[24] *etc.*[25,26] Considering that some of these methods suffer from low yields and high cost of the catalysts, the development of new reaction conditions capable of figuring out a solution to the formidable problems remains highly desirable. Fluorine or trifluoro methyl group at appropriate position of an organic molecule dramatically alters the properties in terms of lipophilicity, lipid solubility, oxidative thermal stability, permeability, oral bio availability thereby enhancement of transport mechanism. In this work, we established a highly effective hydrofluoric acid promoted Biginelli reaction for the preparation of structurally diverse pyrimidinone derivatives bearing trifluoromethyl groups. The anticancer activities of pyrimidinone derivatives were examined against four cancer cell lines such as A549, HepG2, COLO205, DU145 wherein compounds **4e**, **4i**, and **4 m** showed promising results.

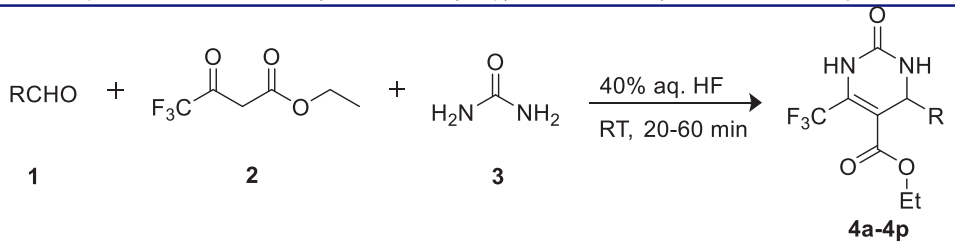
Results and discussion

The initial investigation commenced with aryl aldehyde, trifluoromethyl 1,3-dicarbonyl compound, and urea using commercially available aqueous HF (40%) as solvent medium to prepare the desired 6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives **4a**–**4p** (Scheme 1). A mixture of aryl aldehyde, urea, and trifluoromethyl 1,3-dicarbonyl compound in aq HF (40%) were charged in polypropelene bottle and stirred at ambient temperature to afford the desired products in high yields. Different electron withdrawing or donating groups on the aryl aldehyde were examined and the outcome showed satisfactory functional group tolerance (Table 1).

Cytotoxicity assay

The cytotoxicity of the compounds was determined on the basis of measurement of in vitro growth inhibition of tumor cell lines in 96-well plates by cell-mediated reduction of tetrazolium salt to water insoluble formazan crystals using 5-Fluorouracil as a standard. The cytotoxicity of compounds **4a**–**4p** was assessed against a panel of four different human tumor cell lines: A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185), HepG2 derived from human hepatic carcinoma cells

Table 1. Preparation of 6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives **4a–4p**.



1 2 3 **4a-4p**

No.	Product	R	Time(min)	Yield (%)
1	**4a**	C_6H_5	30	90
2	**4b**	4-$CH_3C_6H_4$	40	87
3	**4c**	4-ClC_6H_4	20	91
4	**4d**	4-BrC_6H_4	25	92
5	**4e**	4-$OCH_3C_6H_4$	20	86
6	**4f**	2-$CH_3C_6H_4$	20	86
7	**4g**	4-FC_6H_4	25	89
8	**4h**	4-$NO_2C_6H_4$	30	85
9	**4i**	3-$CF_3C_6H_4$	20	82
10	**4j**	4-CNC_6H_4	20	82
11	**4k**	2-Furyl	40	85
12	**4l**	2-Thienyl	30	80
13	**4m**	2,4-diFC_6H_3	40	88
14	**4n**	3-$NO_2C_6H_4$	35	79
15	**4o**	Styryl	40	81
16	**4p**	Naphthalene	60	80

Table 2. Anticancer activities of compounds **4a–4p**.

	IC_{50} values in (μg/mL)			
Test Compounds	A549	HepG2	COLO205	DU145
4a	23.2 ± 0.23	31.2 ± 0.25	16.6 ± 0.12	17.4 ± 0.28
4b	15.2 ± 0.11	12.8 ± 0.15	19.2 ± 0.24	12.0 ± 0.12
4c	16.2 ± 0.12	—	18.9 ± 0.33	25.6 ± 0.31
4d	25.8 ± 0.22	12.4 ± 0.33	31.1 ± 0.21	—
4e	9.6 ± 0.15	4.8 ± 0.12	5.1 ± 0.14	4.2 ± 0.19
4f	7.2 ± 0.14	11.4 ± 0.10	10.9 ± 0.20	13.8 ± 0.12
4g	12.9 ± 0.11	17.2 ± 0.27	21.2 ± 0.20	16.5 ± 0.10
4h	11.8 ± 0.19	10.8 ± 0.25	12.4 ± 0.19	9.9 ± 0.29
4i	2.2 ± 0.12	3.1 ± 0.20	2.7 ± 0.22	2.1 ± 0.12
4j	19.5 ± 0.25	17.5 ± 0.10	—	21.5 ± 0.12
4k	32.2 ± 0.22	27.1 ± 0.15	15.7 ± 0.25	22.8 ± 0.12
4l	18.2 ± 0.12	17.1 ± 0.20	18.7 ± 0.28	25.3 ± 0.22
4m	6.1 ± 0.12	4.4 ± 0.24	5.7 ± 0.16	7.8 ± 0.22
4n	11.3 ± 0.13	14.1 ± 0.27	15.8 ± 0.26	17.3 ± 0.32
4o	—	—	—	116.8 ± 0.38
4p	18.4 ± 0.13	17.7 ± 0.30	28.6 ± 0.18	—
5-Fluoro uracil (Standard control)	1.8 ± 0.09	1.9 ± 0.11	1.7 ± 0.08	1.7 ± 0.07

—indicates IC_{50} value >116.8 μg/mL; A549: human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185); HepG2: derived from human hepatic carcinoma cells (ATCC No. HB-8065); COLO205: derived from human colon cancer cells (ATCC No. CCL-222) and DU145: derived from human prostate cancer cells (ATCC No. HTB-81).

(ATCC No. HB-8065), COLO205 derived from human colon cancer cells (ATCC No. CCL-222), and DU145 derived from human prostate cancer cells (ATCC No. HTB-81) using the MTT assay.[27] The IC_{50} values (50% inhibitory concentration) were calculated from the plotted absorbance data for the dose-response curves. IC_{50} values (in μM) are expressed as the average of three independent experiments. Among all the compounds

examined, compounds **4e**, **4i**, and **4 m** showed promising activity (IC_{50} concentration <7.8 µg/mL on all cancer cell lines). The presence of CF_3 group at appropriate position of 6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylates, can enhance the properties of lipid solubility, oxidative thermal stability and thereby leading to a enhancement of transport mechanism. Meanwhile compounds **4 b**, **4f**, **4 g**, **4 h** and **4n** showed moderate activity with IC_{50} concentration <21.2 µg/mL on all cancer cell lines as shown in Table 2.

Conclusion

In conclusion, we have demonstrated a simple and efficient method for the preparation of structurally diverse 6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives under aq. HF (40%) medium. The anticancer activities of all the pyrimidinone derivatives were examined with promising bioactivities.

Experimental section

General procedure

A mixture of aryl aldehyde (0.1 mol), urea (0.1 mol) and trifluoromethyl 1,3-dicarbonyl compound (0.1 mol) in aq HF (40%) were charged in polypropelene bottle and stirred at ambient temperature for a period of 60 min. The reaction progress was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was poured into crushed ice, and the resulted solid was filtered. The solid was washed with water and then sodium bicarbonate solution and dried to afford the product. Please see supporting information for further details (yield and data characterization).

Funding

The authors acknowledge the financial support of National Natural Science Foundation of China [No. 21676129], Jiangsu University scientific research funding [13JD062], and Jiangsu Postdoctoral Foundation [1601034B].

References

[1] (a) Tietze, L. F. *Chem. Rev* **1996**, *96*, 115. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed* **2004**, *43*, 46. (c) Ganem, B. Strategies for Innovation in Multicomponent Reaction Design. *Acc. Chem. Res.* **2009**, *42*, 463. DOI:10.1021/cr950027e.

[2] (a) Kappe, C. O. *Eur. J. Med. Chem* **2000**, *35*, 1043. (b) Litvic, M.; Vecenaj, I.; Ladisic, Z. M.; Lovric, M.; Vinkovic, V.; Filipan-Litvic, M. *Tetrahedron* **2010**, *66*, 3463. DOI:10.1016/S0223-5234(00)01189-2.

[3] Hurst, E. W.; Hull, R. Two New Synthetic Substances Active against Viruses of the Psittacosis-Lymphogranulomatrachoma Group. *J. Med. Pharm. Chem.* **1961**, *3*, 215. DOI:10.1021/jm50015a002.

[4] Ashok, M.; Holla, B. S.; Kumari, N. S. Convenient One Pot Synthesis of Some Novel Derivatives of thiazolo[2,3-b]Dihydropyrimidinone Possessing 4-Methylthiophenyl Moiety and Evaluation of Their Antibacterial and Antifungal Activities. *Eur. J. Med. Chem.* **2007**, *42*, 380. DOI:10.1016/j.ejmech.2006.09.003.

[5] Fewell, S. W.; Smith, C. M.; Lyon, M. A.; Dumitrescu, T. P.; Wipf, P.; Day, B. W.; Brodsky, J. L. Small Molecule Modulators of Endogenous and Co-Chaperone-Stimulated Hsp70 ATPase Activity. *J. Biol. Chem.* **2004**, *279*, 51131. DOI:10.1074/jbc.M404857200.

[6] Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. Small Molecule Inhibitor of Mitotic Spindle Bipolarity Identified in a Phenotype-Based Screen. *Science* **1999**, *286*, 971. DOI:10.1126/science.286.5441.971.

[7] Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. Dihydropyrimidine Calcium Channel Blockers. 4. Basic 3-Substituted-4-Aryl-1,4-Dihydropyrimidine-5-Carboxylic Acid Esters. Potent Antihypertensive Agents. *J. Med. Chem.* **1992**, *35*, 3254. DOI:10.1021/jm00095a023.

[8] Garuti, L.; Roberti, M.; Cermelli, C. Synthesis and Antiviral Activity of Some N-Benzenesulphonylbenzimidazoles. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2525. DOI:10.1016/S0960-894X(99)00429-1.

[9] Kappe, C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog. *Acc. Chem. Res.* **2000**, *33*, 879–888. DOI:10.1021/ar000048h.

[10] McDonald, A. I.; Overman, L. E. Tuning Stereoselection in Tethered Biginelli Condensations. Synthesis of Cis- or Trans-1-Oxo- and 1-Iminohexahydropyrrolo[1,2-c]pyrimidines. *J. Org. Chem.* **1999**, *64*, 1520–1528. DOI:10.1021/jo981972g.

[11] Biginelli, P. Ueber Aldehyduramide Des Acetessigäthers. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 1317–1319. DOI:10.1002/cber.189102401228.

[12] Biginelli, P. Ueber Aldehyduramide Des Acetessigäthers. II. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962–2967. DOI:10.1002/cber.189102402126.

[13] Biginelli, P. *Gazz. Chim. Ital.* **1893**, *19*, 212.

[14] (a) Biginelli, P.; Gazz, P. *Chim. Ital.* **1893**, *23*, 360–416. (b). Biginelli, P. *Gazz. Chim. Ital* **1893**, *23*, 360–413.

[15] Mondal, J.; Sen, T.; Bhaumik, A. Fe3O4@Mesoporous SBA-15: A Robust and Magnetically Recoverable Catalyst for One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones via the Biginelli Reaction. *Dalton Trans.* **2012**, *41*, 6173. DOI:10.1039/c2dt30106g.

[16] Parasuraman, K.; Aswar, S. A.; Muskawar, P. N.; Bhagat, P. R.; Senthil Kumar, S. Development and Efficient 1-Glycyl-3-Methyl Imidazolium Chloride–Copper(II) Complex Catalyzed Highly Enantioselective Synthesis of 3, 4-Dihydropyrimidin-2(1H)-Ones. *J. Organmet. Chem.* **2013**, *723*, 154.

[17] Lal, J.; Sharma, M.; Guptab, S.; Parashara, P.; Sahua, P.; Agarwala, D. D. *J. Mol. Catal. A. Chem.* **2012**, *352*, 31. DOI:10.1016/j.molcata.2011.09.009.

[18] Xu, F.; Huang, D.; Lin, X.; Wang, Y. Highly Enantioselective Biginelli Reaction Catalyzed by SPINOL-Phosphoric Acids. *Org. Biomol. Chem.* **2012**, *10*, 4467. DOI:10.1039/c2ob25663k.

[19] Pourjavadi, A.; Hosseini, S. H.; Soleyman, R. Crosslinked Poly(Ionic Liquid) as High Loaded Dual Acidic Organocatalyst. *J. Mol. Catal. A. Chem.* **2012**, *365*, 55. DOI:10.1016/j.molcata.2012.08.008.

[20] Saha, S.; Moorthy, J. N. Enantioselective Organocatalytic Biginelli Reaction: Dependence of the Catalyst on Sterics, Hydrogen Bonding, and Reinforced Chirality. *J. Org. Chem.* **2011**, *76*, 396. DOI:10.1021/jo101717m.

[21] Kefayati, H.; Asghari, F.; Khanjanian, R. 1-Methylimidazolium Hydrogen Sulfate/Chlorotrimethylsilane: An Effective Catalytic System for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones and Hydroquinazoline-2,5-Diones. *J. Mol. Liq.* **2012**, *172*, 147. DOI:10.1016/j.molliq.2012.01.019.

[22] Narahari, S. R.; Reguri, B. R.; Gudaparthi, O.; Mukkanti, K. Synthesis of Dihydropyrimidinones via Biginelli Multi-Component Reaction. *Tetrahedron Lett.* **2012**, *53*, 1543. DOI:10.1016/j.tetlet.2011.12.134.

[23] Konkala, K.; Sabbavarapu, N. M.; Katla, R.; Durga, N. Y. V.; Vijai Kumar Reddy, T.; Prabhavathi Devi, B. L. A.; Prasad, R. B. N. Revisit to the Biginelli Reaction: A Novel and Recyclable Bioglycerol-Based Sulfonic Acid Functionalized Carbon Catalyst for One-Pot

Synthesis of Substituted 3,4-Dihydropyrimidin-2-(1H)-Ones. *Tetrahedron Lett*. **2012**, *53*, 1968. DOI:10.1016/j.tetlet.2012.02.018.

[24] Shen, Z.-L.; Xu, X.-P.; Ji, S.-J. Brønsted Base-Catalyzed One-Pot Three-Component Biginelli-Type Reaction: an Efficient Synthesis of 4,5,6-triaryl-3,4-dihydropyrimidin-2(1H)-one and Mechanistic Study . *J. Org. Chem*. **2010**, *75*, 1162–1167. DOI:10.1021/jo902394y.

[25] Wu, M.; Yu, J.; Zhao, W.; Wu, J.; Cao, S. One-Pot Synthesis of Difluoromethyl-Containing Dihydropyrimidinones Catalyzed by Yb(PFO)3 under Solvent and Dehydrating Agent Free Conditions. *J Fluorine Chem*. **2011**, *132*, 155. DOI:10.1016/j.jfluchem.2010.12.010.

[26] Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Raj, K. S.; Prasad, A. R. Ultrasound-Accelerated Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones with Ceric Ammonium Nitrate. *J. Chem. Soc, Perkin Trans. 1* **2001**, *16*, 1939.

[27] Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55–63. DOI:10.1016/0022-1759(83)90303-4.