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Synthesis, characterisation of 4-(furan-2-yl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate esters and bioevaluation.

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Abstract:

We report the use of Brønsted acid methane sulfonic acid as a promoter for three component Biginellicyclocondensation reaction of aliphatic aldehydes,1,3-dicarboylcompounds(acetylacetone,acetoaceticester and benzylacetone) and thiourea at RT to afford the corresponding to derivatives of 1,2,3,4-tetrahydropyrimidithione (THPM) in good yields in short span of time . In this study synthesis of some novel Biginelli-type pyrimidines is reported. The prepared compounds are ester derivatives of Methyl 4-(furan-2-yl)-6-methyl-2-thioxo-1, 2,3, 4-tetrahydropyrimidine -5- carboxylate with a simple hetaryl group,furan, at C-4 position of the pyrimidine ring. The structures of all synthesizedcompounds were elucidated by elemental, IR, ^{1}HNMR, ^{13}CNMR spectra.Supplementary to these, they were assayed *in vitro* for their antimicrobialactivity; it was revealed that some synthesized derivatives were exhibitingcompetent biological activity against both gram negative & gram positivebacterial species and fungal microorganisms

Keywords*:* Synthesis; Bintelli pyrimidines; Methanesulphonic acid, antimicrobial activity

INTRODUCTION

Multicomponent reactions (MCR's) are most important to attention and attracting of in Medicinal chemistry and organic chemistry.It is one of the most useful synthetic tools for the enhancement of molecular diversity and complexity in chemistry. Pyrimidine is the six membered heterocyclic ring systems containing two nitrogen atoms ring systems have been described for their biological activity against various microorganisms [1, 2]. Besides this, the chemistry of Pyrimidine has also been reviewed in literature. A number of derivatives of Pyrimidine serve as valuable therapeutic agents [1-5] Considerable interest has been created in the chemistry of Pyrimidine derivatives due to their versatile therapeutic activities. It is also useful in synthesis of various heterocyclic compounds 2-thioxo-1, 2, 3, 4-tetrahydropyrimidineis an interesting moiety which has attractedconsiderable attention of medicinal chemists inthe last

few decades (6). This chemical entitywhich is also called 3,4-dihydropyrimidine-2(1*H*)-thione was introduced tochemistry at the beginning of 1890s by theItalian chemist Pietro Biginelli. A broad range of biological effect, including calcium channel modulation (7, 8), adrenoceptor blocking (9), antitumor (10), antiviral (11), antiinflammatory (12) and antimicrobial (13) activities have been attributed to this class ofheterocyclic compounds

MATERIALS AND METHODS

Chemistry

All chemicals and synthetic grade reagents were used for the synthesis of newly compounds were procured from Fine and SigmaAldrich.Melting points were determined on a Agrawal capillary melting point apparatus and were uncorrected. The^{1}HNMR & ^{13}CNMR spectra ($CDCl_3$) were recorded ona Bruker 400 MHz spectrometer. Chemicalshifts (δ) were reported in ppm downfield fromthe internal standard tetramethylsilane (TMS).Mass spectra were acquired with a Platform IIMass Spectrometer from Micromass.

General procedure for the synthesis of 4-(furan -2- yl) -6- methyl -2- thioxo -1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate esters:

A mixture of furan-2-carbaldehyde **1**(1 mmole), acetoacetate ester **2a-e**(1 mmole) and thiourea (1.3 mmole) was refluxed in 4 ml of absolute ethanol for 6 h.methane sulfonic acid was used as a Bronstd acid. The reaction mixture was filteredoff and the solvent was removed underreduced pressure. The residue was purifiedusing salting out method with acetone andpetroleum ether as solvents (**3a,b**) or bycolumn chromatography using chloroform/methanol as eluent (**3c-e**).

Methyl 4-(furan-2-yl)-6-methyl-2-thioxo-1, 2,3, 4-tetrahydropyrimidine -5- carboxylate (3a*)*

Melting point : 255-256,Yeild: 67 %. Paleyellowsolid.

^{1}HNMR (CDCl3): δ 2.37 (s, 3H,C6-CH3), 3.59 (s, 3H, OCH3), 5.19 (d, *J*=3.6Hz, 1H, C4-H), 6.28 (d, *J*=3.2 Hz, 1H, C5´-H),6.40 (dd, 1H, *J*=3.2 Hz, 1.6 Hz, 1H, C4´-H),7.45 (m, , 1H, C3´-H), 9.47 (d, *J* = 2.0 Hz, 1H,N3-H), 9.89 (s, 1H, N1-H); **^{13}C NMR ($CDCl_3$)δ:** 191.08,165.14,150.77,141.95,128.48,125.19,110.26,109.42,54.47,50.36,18.33**. Mol**. **formula** : $C_{11}H_{12}N_2O_3S$. **LCMS (m/z): 251.41. Elemental analysis**: Calculated: C-52.37, H-4.79,N-11.10. Obtained: C-52.32, H-4.78,N-11.18.

Ethyl 4-(furan-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3b)

Melting point: 225-227, Yeild: 64% .Pale yellow solid.

^{1}HNMR (CDCl3): δ 1.19 (t, *J*=6.8 Hz, 3H,CH2CH3), 2.34 (s, 3H, C6-CH3), 4.08-4.14 (m,2H, CH2CH3), 5.29 (d, *J*=4.0 Hz, 1H, C4-H),6.20 (d, *J*=2.8 Hz, 1H, C5´-H), 6.44 (m, 1H,C4´-H), 7.64 (m, 1H, C3´-H), 9.69 (bs, 1H,N3-H), 10.45 (s, 1H, N1-H); **^{13}C NMR ($CDCl_3$)δ:** 188.7,164.8,150.6,141.7,129.6,122.3,110.9,107.6,61.8,53.1,17.7,14.2**. Mol**. **Formula:** $C_{12}H_{14}N_2O_3S$.**LCMS (m/z):** 266.32. **Elemental analysis**: Calculated: C-54.12, H-5.30,N-10.52. Obtained: C-54.05, H-5.29,N-10.61.

Iso-Propyl 4-(furan-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3c*)*

Melting point: 191-192**, Yeild**: 68. Pale yellow solid.

^{1}HNMR (CDCl3): δ 1.12 (d, *J*=6.0 Hz, 3H,CH(CH3)2), 1.23 (d, *J*=6.4 Hz, 3H, CH(CH3)2),2.30 (s, 3H, C6-CH3), 4.92 (heptet, , 1H,CH(CH3)2), 5.28 (d, *J*=4.0 Hz, 1H, C4-H),6.20 (d, *J*=3.2 Hz, 1H, C5´-H), 6.44 (m, 1H,1H, C4´-H), 7.64 (m, 1H, C3´-H), 9.67 (bs,1H, N3-H), 10.42 (s, 1H, N1-H); **^{13}C NMR ($CDCl_3$)δ:** 186.2,163.3,148.2,141.5,128.6,120.3,109.7,107.3,66.1,54.7,20.9,19.7,17.1. **Mol**. **Formula:** $C_{13}H_{16}N_2O_3S$ **LCMS (m/z):** 280.34 **Elemental analysis**: Calculated: C-55.70, H-5.75,N-9.94.Obtained: C-55.66, H-5.74,N-10.03.

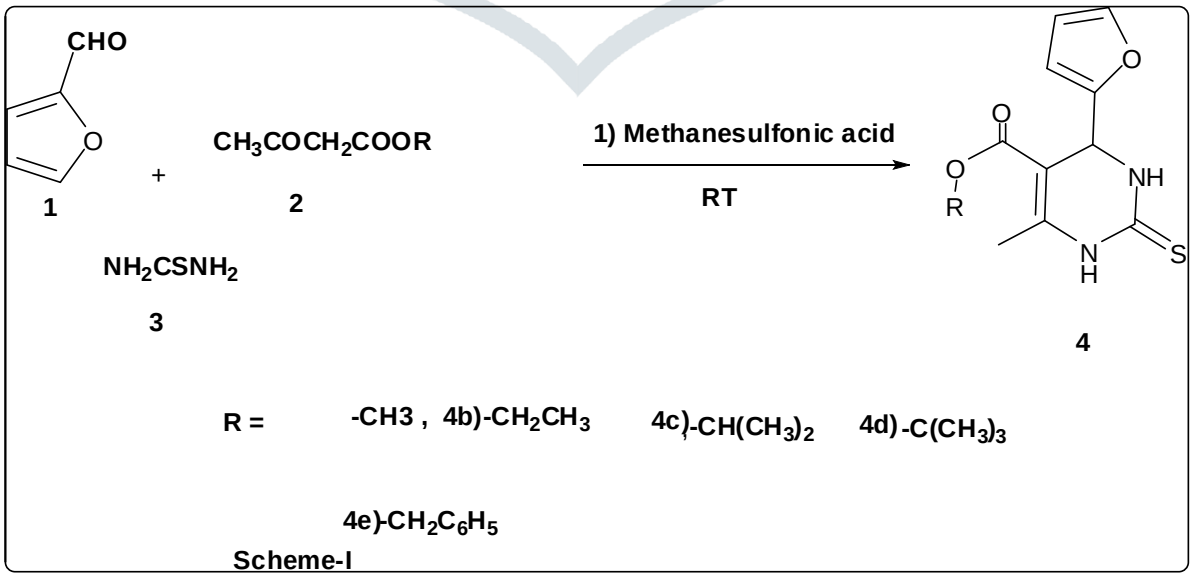
Tert-Butyl4-(furan-2-yl)-6-methy-l-2-thioxo-1,2,3,4-tetrahydropyrimidine-5- carboxylate (3d)

Melting point: 196-198 .Yeild: 63. Pale yellow solid.

^{1}HNMR (CDCl3): δ 1.35 (s, 9H,CH(CH3)3), 2.24 (s, 3H, C6-CH3), 5.17 (s, 1H,C4-H), 6.13 (bs, 1H, C5´-H), 6.39 (m, 1H, 1H,C4´-H), 7.58 (bs, 1H, C3´-H), 9.55 (bs, 1H,N3-H), 10.28 (s,1H,N1-H);**^{13}CNMR($CDCl_3$)δ:**186.7,165.01,142.4,140.3,134.5,122.5,109.4,72.3, 55.7, 28.9, 28.1,27.6,17.9. **Mol**. **Formula:** $C_{14}H_{18}N_2O_3S$ **LCMS (m/z)**: 294.37 **Elemental analysis**: Calculated: C-57.12, H-6.16,N-9.52. Obtained: C-57.07, H-6.15,N-9.59.

Benzyl 4- (furan-2-yl) -6- methy l- 2- thioxo-1, 2, 3, 4-tetrahydropyrimidine-5- carboxylate (3e): Melting point: 168-169, Yeild: 66%. Pale yellow solid.

^{1}HNMR (CDCl3): δ 2.30 (s, 3H,C6-CH3), 5.06 (doublet, *J*=12.8 Hz, Ha,CHaHbC6H5), 5.12 (doublet, *J*=12.8 Hz,Hb,CHaHbC6H5), 5.27 (d, *J*=3.6 Hz, 1H, C4-H),6.11 (d, *J*=3.2 Hz, 1H, C5´-H), 6.38 (dd, 1H,*J*=3.2 Hz, 1.6 Hz, 1H, C4´-H), 7.22-7.33 (m,5H, C6H5), 7.59 (dd, *J*=1.6, *J*=0.8, 1H, C3´-H),9.66 (m, 1H, N3-H), 10.46 (s, 1H, N1-H). **^{13}C NMR ($CDCl_3$)δ:** 190.4,166.3,148.2141.4,129.5,128.9,128.1,127.4,126.7,124.8,110.5108.7,60.7,56.9,16.8.**Mol**. **Formula:** $C_{17}H_{16}N_2O_3S$ .. **LCMS (m/z):** 328.39. **Elemental analysis**: Calculated: C-62.18, H-4.91,N-8.53. Obtained: C-62.11, H-4.89,N-8.63.



Scheme-I

***Antimicrobial assay*:**

The antimicrobial activities were determined using agar–cup methodby measuring the zone of inhibition in mm. All newly synthesized compounds werescreened *in vitro* for their antibacterial activity against Gram positive species (*Bacillussubtilis*, *Bacillus megaterium*) and Gram negative species (*Escherichia coli*, *Pseudomonasaeruginosa*), while antifungal activity was tested against *Aspergillus niger* and *C. albicans* atconcentration of 75 µg/ml. Streptomycin was used as a standard drug for antibacterialscreening, while Imidil was used as a standard drug for antifungal screening and solventDMSO was used as a control. Each experiment was made in triplicate and the averagereading was taken. The results are summarized in Table-I.

Table-I Antimicrobial activity screening activity synthesized scaffold

CompoundCode	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
5a	11	12	10	11	10	09
5b	20	19	14	20	08	10
5c	22	19	14	21	08	08
5d	21	20	15	22	17	20
5e	17	11	10	14	10	09
Amoxycilline	30	35	31	28	NA	NA
Ketoconazole	NA	NA	NA	NA	20	25
DMSO	---	----	---	---	---	---

Result & Discussion:

The one-pot three-component method showed some crucial advantages, such as short reactiontime, excellent yield and high purity, which makes it more efficient and broadly applicable. Thepercentage yield and the reaction time of the one-pot three-components method in comparison with theone-pot three-component one to produce compound **6** was found to be 91/66% and 1 h/10 h,respectively (Scheme 1).

All newly synthesized compounds can be obtained at room temperature. These target compounds can be obtained, we used to organic acid catalyst is PTS. This organic catalyst can be used to develop the reaction conditions and reaction is completed maximum 3 hours. The rate of reaction increased by using this catalyst. We used various heteroaromatic carb aldehydes such as indole-3-carbaldehyde,furan aldehyde , pyrrole aldehyde , thiophenal, pyridine -2-carbaldehyde. Consequently nitrogen containing five membere heterocyclic compound such as furan and pyrrole aldehydes react with 2-aminobenzimidazole to obtained more yield and rate of reaction increases and completion of the reaction before 30 min compared to that thiophene aldehyde and pyridine -2-

carbaldehyde react with 2-aminobenzimidazole. We are using methane sulfonic acid, the reaction workup is easily. (**Scheme-I)**

All the synthesized compounds were examined anti bacterial activity as well as antifungal. Indole -3-carbaldehyd showed poor activity. Furan 2-carbaldehyde and pyrrole aldehyde showed good activity where as thophenal and pyridine -2-carbaldehyde showed moderate actity as shown in Table-I.

4. Conclusions

In conclusion, we have reported the synthesis of some novel heterocyclic pyrazolopyrimidinopyridinesand related compounds. Five of the newly synthesized compounds have beenscreened for their biological activities against two Gram positive, two Gram negative bacteria, aswell as two fungal strains. Most of the tested compounds showed activities against the strains used.Compound **5d** exhibited to be the most active potent compound of all those used.

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References:

1. Jain R , Jain S, Gupta R C, Anand N, Dutta G P, Puri S K, *Indian J. Chem.*,1994,**338**, 251.

2. Mohammed A, Abdel-Hamid N, Maher F, Farghaly A, *Czech. Chem. Commun.*,1992,**57(7)**, 1547.

3. Cairns H, Cox D, Gould K J, Ingall A H, Suschitzky J L, *J. Med. Chem.*,1985,**28(12),** 1832 .

4. Croisy-Delcey M, Coroisy A, Carrez D, C Huel, A Chiaroni, P Ducrot, E Bisagni,Jin, G Leclercq, *Bioorg. Med. Chem.*,2000, **8(ii)**, 2629.

5. Dlugosz A, Dus D, *Farmaco.*,1996, **51**, 367.

6. Kappe CO. Biologically active dihydropyrimidonesof the Biginelli-type-A literature survey. Eur J MedChem. 2000;35:1043-1052.

7. Biginelli P. Aldehyde-urea derivatives of aceto- andoxaloacetic acids. Gaz Chim Ital. 1893;23:360-413.

8. Rovnyak GC, Atwal KS, Hedberg A, Kimball SD,Moreland S, Gougoutas JZ, *et al*. Dihydropyrimidinecalcium channel blockers. 4. Basic 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid esters.Potent antihypertensive agents. J Med Chem.
1992;35:3254-3263.

9. Barrow JC, Nantermet PG, Selnick HG, Glass KL,Rittle KE, Gilbert KF, *et al*. *In vitro* and *in vivo*evaluation of dihydropyrimidinone C-5 amides aspotent and selective α1A receptor antagonists for thetreatment of benign prostatic hyperplasia. J MedChem.2000;43:2703-2718.

10. Klein E, De Bonis S, Thiede B, Skoufias DA,Kozielski F, Lebeau L. New chemical tools for investigating human mitotic kinesin Eg5. BioorgMed Chem. 2007;15:6474-6488.

11. Zabihollahi R, Vahabpour B, Sedaghati B,Hartoonian C, Sadat SM, Soleymani M, *et al.*

Evaluation of the in vitro antiretroviral potential ofSome Biginelli-Type Pyrimidines. Acta Virologica.2012;56:11-18.

12. Bahekar SS, Shinde DB. Synthesis and antiinflammatoryactivity of some [4,6-(4-substituted aryl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid derivatives. Bioorg Med Chem Lett.2004;14:1733-1736.

13. Sedaghati B, Fassihi A, Arbabi S, Ranjbar M,Memarian HR, Saghaie L, *et al.* Synthesis and antimicrobial activity of novel derivatives ofBiginelli pyrimidines. Med Chem Res. In Press.