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A Facile Synthesis of Piperazine Derivatives and their Pharmacological Profile

K.S. Thriveni, Basavaraj Padmashali*, M.B. Siddesh, C. Sandeep and B.C. Goudarshivannanavar

*Department of Chemistry, Sahyadri Science College (Autonomous), Kuvempu University, Shimoga-577203, Karnataka, **INDIA**

Email: basavarajpadmashali@yahoo.com

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ABSTRACT

*Some new (2-tert-butylpyrimidin-5-yl)[4-(substituted-2-ylcarbonyl)piperazin-1-yl]methanones **4a-g** and (2-tert-butylpyrimidin-5-yl)[4-(5-substituted-1,3-benzoxazol-2-yl)piperazin-1-yl]methanones **5a-c** has been synthesized using piperazine containing 2-tert-butylpyrimidine as core moiety with different heterocyclic carboxylic acids and 5-substituted-2-(methylsulfanyl)-1,3-benzoxazoles. The newly synthesized compounds were characterized by spectroscopic evidences such as IR, ^1H NMR, mass spectrum and CHN elemental analysis. Preliminary pharmacological observations revealed that some of the derivatives shown promising in vitro antibacterial and anthelmintic activity.*

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Keywords: Piperazine, pyrimidine, furan, thiophene, HATU, antibacterial activity, anthelmintic activity.

INTRODUCTION

Piperazine is a vital heterocyclic nucleus which is well known for its wide biological profile. Piperazine derivatives are also associated with an extensive array of pharmacological activities including antimicrobial [1-5], analgesic [6], anticancer [7], anti-inflammatory agents [8]. The aim of research is to develop new bioactive entities, especially with antimicrobial activities bearing a different piperazine derivatives nucleus. Numerous piperazine derivatives like aryl amide have been prepared. Above piperazine derivatives containing a wide spectrum of biological activities viz. anti-inflammatory, antibacterial [9,10], antimalarial [11], orally bioavailable cannabinoid receptor 2 (CB2) agonists [12], dual vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1 inhibitors [13], DNA gyrase inhibitor [14] and orally active non-peptidic inhibitors of human neutrophil elastase [15]. Aromatic acid amides having electron-withdrawing group shows good biological activity such as anti-bacterial, antifungal and 5-HT3R binding affinities [16] etc. Taking in view of the applicability and chemical diversity in the molecular frame work in order to interest for synthesis, spectral studies and therapeutic activity of some new piperazine derivatives.

MATERIALS AND METHODS

All the melting points were determined in an open capillary and were uncorrected. IR spectra were recorded on Bruker alpha FT IR spectrophotometer, ^{1}H NMR spectra were measured on Bruker AV 400MHZ using $CDCl_3$ and DMSO as solvent. Chemical shifts are expressed in δ ppm. Mass spectra were performed on a Joel JMS-D 300 mass spectrometer operating at 70 eV. All the reactions were followed and checked by TLC, and further purification was done by column chromatography. All the reagents used were of AR grade and they were again purified by distillation.

Preparation of *tert*-butyl 4-[(2- *tert*-butyl pyrimidin-5-yl) carbonyl] piperazine-1-carboxylate 2:

A mixture of 2-*tert*-butylpyrimidine-5-carboxylic acid **1** (0.18 g, 0.001 mol) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorohosphate (HATU coupling reagent) (0.19g, 0.0005 mol) were stirred for half an hour in dimethyl formamide (2mL) in presence of triethylamine (0.30 mL, 0.003 mol) then *tert*-butyl piperazine-1-carboxylate (0.18 g, 0.01 mol) was added and the reaction mixture was warmed to 50°C for 3 hours. The reaction mixture was then diluted with water and extracted with ethyl acetate. Then ethyl acetate was evaporated to dryness to get pure compound **2**.

***tert*-Butyl 4-[(2- *tert*-butyl pyrimidin-5-yl)carbonyl]piperazine-1-carboxylate 2:** IR (KBr): 1650 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ, 3.60-3.63 (4H, t, $2CH_2$), 3.37-3.44 (4H, t, $2CH_2$), 1.34 (9H, s, $3CH_3$), 1.39 (9H, s, $3CH_3$), 8.90-8.91 (2H, s, Ar-H); MS: m/z 349.

Procedure for the preparation of (2-*tert*-butylpyrimidin-5-yl)(piperazin-1-yl)methanone 3: Deprotection of Boc group was achieved by using 1,3-Dioxane.HCl. A mixture of *tert*-butyl 4-[(2- *tert*-butyl pyrimidin-5-yl) carbonyl] piperazine-1-carboxylate **(2)** (3.48g, 0.01mols) was taken in excess of 1,4-Dioxane.HCl (25 ml) and refluxed for 5 h. The reaction was monitored by TLC 1,4-Dioxane.HCl was distilled off, to obtain the compound **(3)**.

(2-*tert*-Butylpyrimidin-5-yl)(piperazin-1-yl)methanone 3: IR (KBr): 1655 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ, 3.54-3.56 (4H, t, $2CH_2$), 3.29-3.30 (4H, t, $2CH_2$), 1.35 (9H, s, $3CH_3$), 8.97-8.99 (2H, s, Ar-H);MS m/z: 249.

Preparation of (2-*tert*-butylpyrimidin-5-yl)[4-(substituted-2-ylcarbonyl)piperazin-1-yl]methanone 4a: A mixture of furan-2-carboxylic acid (1.12 g, 0.01 mol) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorohosphate (HATU coupling reagent) (1.9 g, 0.005 mol) were stirred for half an hour in DMF (10 mL) in presence of triethylamine (3.03 mL, 0.03 mol). Then, (2-*tert*-butylpyrimidin-5-yl)(piperazin-1-yl)methanone **3** (2.49 g, 0.01 mol) was added and the reaction mixture was warmed to 50°C for 5 hours. The completion of the reaction was monitored by TLC. The reaction mixture was then diluted with water and extracted with ethyl acetate. Then ethyl acetate was evaporated to dryness to get pure compound **4a**. Similarly, the compounds **4b-g** were prepared using different carboxylic acids.

(2-*tert*-Butylpyrimidin-5-yl)[4-(furan-2-ylcarbonyl)piperazin-1-yl]methanone (4a): IR (KBr): 1650 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ 3.63-3.66 (4H, t, $2CH_2$), 3.44-3.47 (4H, t, $2CH_2$), 1.36 (9H, s, $3CH_3$), 7.78-9.00 (5H, m, Ar-H); MS m/z: 343.

(2-*tert*-Butylpyrimidin-5-yl)[4-(pyridin-2-ylcarbonyl)piperazin-1-yl]methanone (4b): IR (KBr): 1645 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ 3.65-3.67 (4H, t, $2CH_2$), 3.39-3.40 (4H, t, $2CH_2$), 1.32 (9H, s, $3CH_3$), 7.80-8.99 (6H, m, Ar-H); MS m/z: 359.

(2-*tert*-Butylpyrimidin-5-yl)[4-(thiophen-2-ylcarbonyl)piperazin-1-yl]methanone (4c): IR (KBr): 1670(C=O) cm^{-1}; ^{1}H NMR (DMSO): δ 3.67-3.70 (4H, t, $2CH_2$), 3.46-3.49 (4H, t, $2CH_2$), 1.35 (9H, s, $3CH_3$), 7.75-8.99 (5H, m, Ar-H); MS m/z: 354.

(2-*tert*-Butylpyrimidin-5-yl)(4-phenylpiperazin-1-yl)methanone (4d): IR (KBr): 1655 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ 3.50-3.53 (4H, t, $2CH_2$), 3.30-3.33 (4H, t, $2CH_2$), 1.38 (9H, s, $3CH_3$), 7.77-8.79 (7H, m, Ar-H); MS m/z: 353.

(2-*tert*-Butylpyrimidin-5-yl)[4-(4-chlorophenyl)piperazin-1-yl]methanone (4e): IR (KBr): 1650 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ 3.70-3.73 (4H, t, $2CH_2$), 3.39-3.40 (4H, t, $2CH_2$), 1.35 (9H, s, $3CH_3$), 7.75-8.99 (6H, m, Ar-H); MS m/z: 388.

(2-*tert*-Butylpyrimidin-5-yl)[4-(4-bromophenyl)piperazin-1-yl]methanone (4f): IR (KBr): 1648 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ 3.84-3.86 (4H, t, $2CH_2$), 3.39-3.40 (4H, t, $2CH_2$), 1.34 (9H, s, $3CH_3$), 7.75-8.99 (6H, m, Ar-H); MS m/z: 432.

(2-*tert*-Butylpyrimidin-5-yl)[4-(2-chlorophenyl)piperazin-1-yl]methanone (4g): IR (KBr): 1635 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ 3.84-3.86 (4H, t, $2CH_2$), 3.39-3.40 (4H, t, $2CH_2$), 1.35 (9H, s, $3CH_3$), 7.74-8.99 (6H, m, Ar-H); MS m/z: 388.

General procedure for the preparation of (2-*tert*-Butylpyrimidin-5-yl)[4-(5-substituted-1,3-benzoxazol-2-yl)piperazin-1-yl]methanone (5a-c): (2-*tert*-Butylpyrimidin-5-yl)(piperazin-1-yl)methanone **(3)** (0.01moles) and 5-substituted-2-(methylsulfanyl)-1,3-benzoxazole (0.01 mols) in DMF (10 ml) was refluxed for 12 h. The reaction mixture was poured into ice cold water, the product separated was filtered off and recrystallized from ethanol to get pure **(5a-c)**.

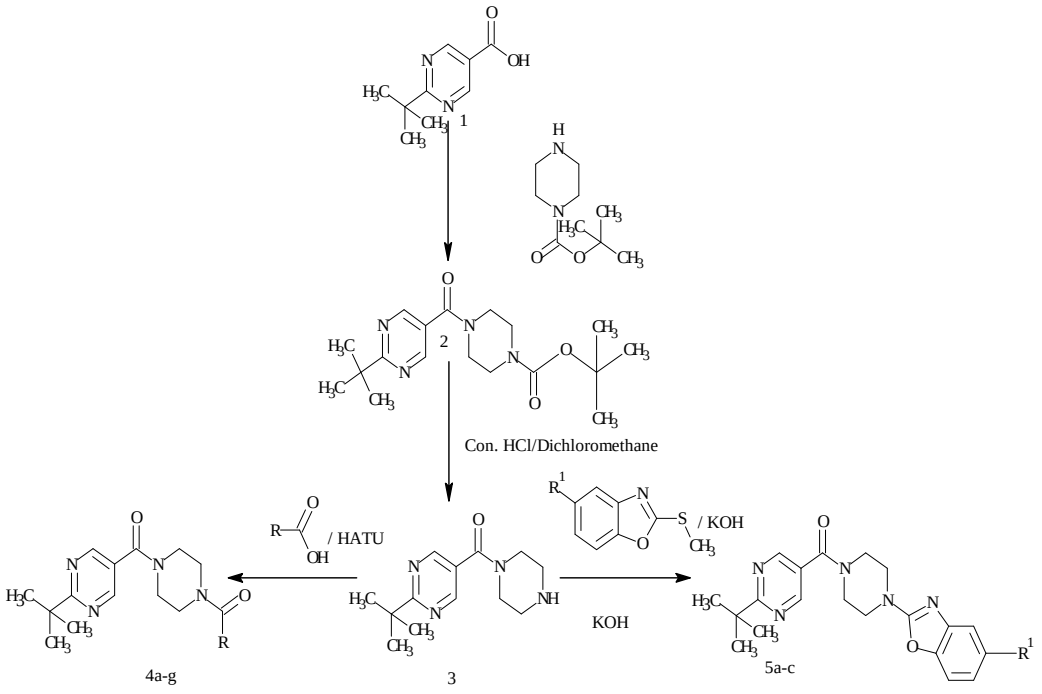
(2-*tert*-Butylpyrimidin-5-yl)[4-(5-chloro-1,3-benzoxazol-2-yl)piperazin-1-yl]methanone (5a): IR (KBr): 1655 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ, 3.35-3.38 (4H, t, $2CH_2$), 3.58-3.61 (4H, t, $2CH_2$), 1.33 (9H, s, $3CH_3$), 7.29-8.10 (5H, m, Ar-H); MS m/z: 402.

[4-(1,3-Benzoxazol-2-yl)piperazin-1-yl](2-*tert*-butylpyrimidin-5-yl)methanone (5b): IR (KBr): 1660 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ, 3.42-3.45 (4H, t, $2CH_2$), 3.55-3.58 (4H, t, $2CH_2$), 1.34 (9H, s, $3CH_3$), 7.35-8.00 (6H, m, Ar-H); MS m/z: 366.

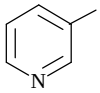
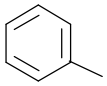
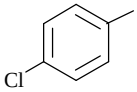
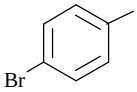
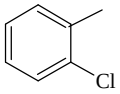
(2-*tert*-Butylpyrimidin-5-yl)[4-(5-nitro-1,3-benzoxazol-2-yl)piperazin-1-yl]methanone (5c): IR (KBr): 1664 (C=O) cm^{-1}; ^{1}H NMR (DMSO): δ, 3.39-3.42 (4H, t, $2CH_2$), 3.60-3.63 (4H, t, $2CH_2$), 1.36 (9H, s, $3CH_3$), 7.37-8.25 (5H, m, Ar-H); MS m/z: 411.

Biological studies

Antibacterial activity: Newly synthesized compounds **4a-f** and **5a-c** was screened for their antibacterial activity. Compounds were prepared using DMSO at 40μg/ml concentration and were tested against *Staphylococcus aureus* (Gram +ve), *Bacillus subtillis* (Gram +ve), *Escherichia coli* (Gram -ve) and *Salmonella paratyphi-A* (Gram -ve) bacterial stains by cup-plate method [17] using Procaine penicillin and Streptomycin as standard drugs. The compounds showed varying degree of antibacterial activity. The results are shown in table 2**.**



Scheme 1

Compound	R	Compound	R^1
4a		5a	Cl
4b		5b	H
4c		5c	NO_2
4d			
4e			
4f			
4g			

Anthelmintic activity: The newly synthesized compounds **4a-f** and **5a-c** was screened for their anthelmintic studies were carried out against Pheritima posthuma species of earthworms by Garg and Atal method [18] at 4 mg/ml concentration and Albendazole was used as standard drug. The compounds showed varying degree of analgesic activity. The results are shown in table 3

RESULTS AND DISCUSSION

Initially *tert*-Butyl 4-[(2- *tert*-butyl pyrimidin-5-yl)carbonyl]piperazine-1-carboxylate **2** was prepared from 2-*tert*-butylpyrimidine-5-carboxylic acid **1** and *tert*-butyl piperazine-1-carboxylate in the presence of HATU coupling reagent and triethylamine. Further deprotection of Boc group gave the (2-*tert*-butylpyrimidin-5-yl)(piperazin-1-yl)methanone **3**. The unprotected secondary amino group of **3** was made to react with different substituted heterocyclic carboxylic acids in the presence of triethylamine and HATU coupling reagent to get new acid amides containing *tert*-butyl pyrimidine nucleus **4a-f** in good yield and also compound **3** treated with 5-substituted-2-(methylsulfanyl)-1,3-benzoxazoles to get (2-*tert*-butylpyrimidin-5-yl)[4-(5-substituted-1,3-benzoxazol-2-yl)piperazin-1-yl]methanones **5a-c**. Newly synthesized compounds were tested for their antibacterial activity and anthelmintic activity.

The IR spectrum of a representative compound **4a** and **5a** shows C=O absorption vibration stretching in the range 1650 and 1655 cm^{-1} respectively. Aromatic C-H band displays at 3077-3018 cm^{-1}. A weak band at 1576-1555 represents C=C bond of the aromatic ring.

In the ^1H NMR spectrum of a representative compound **4a** five aromatic protons appears as a multiplet in the range 7.78-9.00 ppm. Eight protons of piperazine methylene groups (CH_2) appears in the range 3.63-3.66 (t, 4H) and 3.44-3.47 (t, 4H) and nine protons of three CH_3 groups appears in the range 1.36 (s, 9H).

The compound **5a** five aromatic protons appear as a multiplet in the range 7.29-8.10 ppm. Eight protons of piperazine methylene groups (CH_2) appears in the range 3.35-3.38 (t, 4H) and 3.58-3.61 (t, 4H) and nine protons of three CH_3 groups appears in the range 1.33 (s, 9H). These evidences confirm the formation of the compounds.

From the table 2, Compounds **4a**, **4c**, **4f** and **5a** were found to have comparable potency against *Staphylococcus aureus*, *Bacillus subtillis*, *Escherichia coli* and *Salmonella paratyphi-A* compared to standard drugs Procaine penicillin and Streptomycin while some of them have less potency against tested strains. From the Table 3, Compounds **4a**, **4b**, **4d** and **5a** were found to possess good anthelmintic activity.Procaine penicillin and Streptomycin is used as a positive controls and the zone of inhibition is expressed in mm.

Table 1: Characterisation data of the synthesised compounds

Compound	Yield (%)	m.p°C	Mol. formula (Mol.Wt)	Found % (Cacld)		
				C	H	N
2	65	200	$C_{18}H_{28}N_4O_3$ (348.43)	61.90 (61.99)	8.00 (8.03)	16.00 (16.07)
3	50	185	$C_{13}H_{20}N_4O$ (248.32)	62.79 (62.82)	8.00 (8.05)	22.50 (22.55)
4a	72	177	$C_{18}H_{22}N_4O_3$ (342.39)	63.00 (63.08)	6.39 (6.42)	16.30 (16.35)
4b	69	208	$C_{18}H_{22}N_4O_2S$ (358.45)	60.20 (60.25)	6.06 (6.13)	15.60 (15.62)
4c	71	210	$C_{19}H_{23}N_5O_2$ (353.41)	64.45 (64.51)	6.45 (6.50)	19.75 (19.80)
4d	68	196	$C_{20}H_{24}N_4O_2$ (352.43)	68.00 (68.09)	6.46 (6.80)	15.82 (15.88)
4e	71	202	$C_{20}H_{23}ClN_4O_2$ (386.87)	60.90 (66.95)	6.36 (6.41)	15.55 (15.62)
4f	65	180	$C_{20}H_{23}BrN_4O_2$ (431.32)	68.00 (68.09)	6.72 (6.80)	15.80 (15.88)
4g	73	175	$C_{20}H_{23}ClN_4O_2$ (386.87)	68.13 (68.18)	5.34 (5.38)	16.69 (16.74)
5a	45	198	$C_{20}H_{22}ClN_5O_2$ (399.87)	59.96 (60.01)	5.54 (5.50)	13.95 (14.00)
5b	60	179	$C_{20}H_{23}N_4O_2$ (365.42)	65.60 (65.67)	6.23 (6.29)	15.28 (15.32)
5c	50	207	$C_{20}H_{22}N_6O_4$ (410.42)	58.40 (58.47)	5.30 (5.36)	20.40 (20.46)

Table 2: Antibacterial activity of the compounds 4a-g and 5a-c

Compounds	Mean zone of inhibition (in mm)			
	S. aureus **(40µg/ml)**	***B. subtillis*** **(40µg/ml)**	***E. coli*** **(40µg/ml)**	***S. paratyphi-A*** **(40µg/ml)**
4a	16	15	14	16
4b	14	12	13	16
4c	16	16	15	14
4d	15	13	13	15
4e	14	14	15	14
4f	17	15	16	14
4g	16	12	12	13
5a	14	16	15	16
5b	14	13	13	14
5c	14	14	13	15
Procaine penicillin	20	20	-	-
Streptomycin	-	-	20	23

Table 3: Anthelmintic activity of the compounds 4a-g and 5a-c

Compounds	Mean paralyzing time+ S.D. *(min)	Mean death time+ S.D. *(min)
4a	14.59 ± 0.06	21.58 ± 0.14
4b	13.11± 0.03	21.31 ± 0.26
4c	14.05 ± 0.13	36.38 ± 0.16
4d	16.88 ± 0.22	27.67 ± 0.11
4e	16.06 ± 0.05	31.56 ± 0.15
4f	17.04 ±0.65	29.32 ± 0.91
4g	14.06 ± 0.15	33.38 ± 0.10
5a	15.63 ± 0.16	26.18 ± 0.20
5b	13.11 ± 0.18	34.05 ± 0.30
5c	17.12 ± 0.11	32.74 ± 0.36
Albendazole	9.35 ± 0.12	21.15 ± 0.17

n=5, $p<0.05$, Concentration = 4 mg ml^{-1}

APPLICATIONS

In the present study the derivatives which we have synthesized were screened for their antibacterial activity and anthelmintic activity, which are promising as active pharmacophore. Further studies are undergoing.

CONCLUSIONS

In the present research we synthesized some novel acid amides containing piperazin-1-yl(2-tert-butyl pyrimidin-5-yl)methanone nucleus compounds and they are initially screened for their their antibacterial and anthelmintic activities . Thus the study was found very useful to identify antibacterial and anthelmintic activities targets among the synthesized piperazine derivatives.

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