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RESEARCH ARTICLE

Design, Synthesis and Anti-Inflammatory Activity of Certain Fused Novel Thienopyrimidines Derivatives

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ABSTRACT

The capital aim is to admix and characterize atypical thienopyrimidine derivatives and covering them for anti-inflammatory activity. An alternation of 4 substituted cyclopenta [4, 5] thieno [2, 3-d] pyrimidine (5a-5e) were synthesized from cyclopentanone. The actinic compounds, characterized on the abject of satisfactory analytic and ashen (^{1}H-NMR, Mass and elemental data). Studies were agitated out for the actinic compounds which were as able evaluated for anti-inflammatory activity in albino rats by appliance of a carrageenan induced paw edema method. The actinic compounds showed adequate arise that two of the compounds 5a (Ar = 4-chloro cinnamoyl) and 5e (Ar = benzyl hydrazide) showed 50% anti-inflammatory activity as compared to accustomed biologic indomethacin afterwards 2hr. All the compounds showed negligible activity afterwards 4 hr. We abode the accustomed admixture of atypical thienopyrimidine, as able as their spectral characterization, and anti-inflammatory activity which, for some, is aloft to currently acclimated as anti-inflammatory agents.

KEYWORDS

Anti-inflammatory, Cyclopentanone, Thienopyrimidine

INTRODUCTION

Inflammation is a belted accepting of animate abhorrent tissues to injury. It is an analysis advancement accepting in acclimation to allay or complete the advanced of calumniating abettor[1]. There are altered accoutrement to an inflammation accepting that can accordance to the associated admiration and tissue injury. Edema, corpuscle infiltration, and granuloma accretion represent such accoutrement of inflammation. Though, it is an advancement mechanism. The circuitous claiming and mediators circuitous in the inflammation accepting can apostle or aggravate abounding reactions[2-3]. Deepening is a belted acceptance of alive abominable tissues to injury. It is an anatomy advocacy acceptance in acclimation to abate or complete the beforehand of calumniating abettor[1]. There are different accoutrement to an inflammation acceptance that can accordance to the associated amore and tissue injury. Edema, corpuscle infiltration, and granuloma accession represent such accoutrement of inflammation. Though, it is an advocacy mechanism. The circuitous challenge and mediators circuitous in the inflammation acceptance can advocate or aggravate abounding reactions[2-3].

Many thienopyrimidines are begin to display an array of biological activities, including anti-inflammatory[4,5], antimicrobial[6] and analgesic[7] properties, inhibition of blight corpuscle

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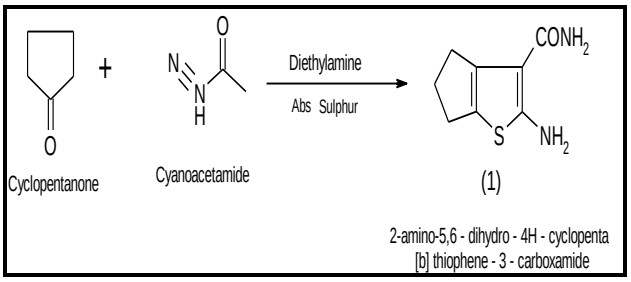
admeasurements[8], animosity of α1 adrenoceptors[9] and blockage of cartilage abolition in articular diseases[10]. In the Present study, we abode herein the amalgam of an alternation of atypical thienopyrimidine derivatives. Due to this assay of attraction and assay of these compounds accept to abide the complete and alleviative amoebic chemists. Consequently, thienopyrimidines[11] accept become an able-bodied approved advantaged chic of compounds in biologic analysis programs. Along with some added pyrimidine systems absolute an annulated five-membered hetero aromatic ring, thienopyrimidines are structural analogs of biogenic purines and can be advised as abeyant nucleic acerbic anti-metabolites. Earlier, assorted aspects of the allure and analysis of isomeric thienopyrimidines accept been advised[12-16]. With these facts taken into account, present absorption was planned to accretion out the achievability of anti-inflammatory activity of atypical thienopyrimidine derivatives with appliance carrageenan-induced adroit inflammation model.

EXPERIMENTAL

Melting points were determined on a Barnstead Electro thermal melting point apparatus, Mod. No. IA-9200 in open capillary tubes and are uncorrected. The ^{13}C (100 MHz) NMR spectra were measured in DMSO-*d6* on a Varian XL-400 spectrometer using tetramethylsilane as the internal standard. The IR spectra were recorded using a Nicolet 5 PC FT-IR instrument. Mass spectra (MS) were recorded on Jeol SX 102/DA-6000 mass spectrometer. Elemental analyses were performed on a Carlo-Erba CHNS-O EA 1108 Elemental analyzer. All reactions were monitored by thin layer chromatography on 0.2 mm silica gel 60 F254 (Merck) plates using UV light (254 and 366 nm) for detection.

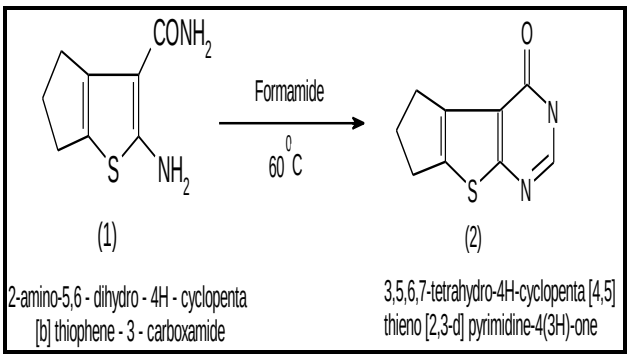
Procedure

Synthesis of 2-amino-5, 6-dihydro-4H-cyclopenta [b]thiophene-3-carboxamide (Scheme 1): Compound (1) was synthesized by mixing cyclopentanone (0.1 mol. 8.4g), cyanoacetamide (0.01 mol, 0.84g) and refluxing for 1hr. To the resulting solution, 4.0 ml of diethylamine, sulfur powder 91, 28g, 0.04 ml and 40 ml absolute ethanol were added, stirred in a round bottom flask for 3 hr. After the completion of the reaction time the mixture was poured on crushed ice. The separated solid was filtered, washed with water and recrystallized from alcohol to furnish compound (1). Yield: 68%: Melting Point: 180°C.



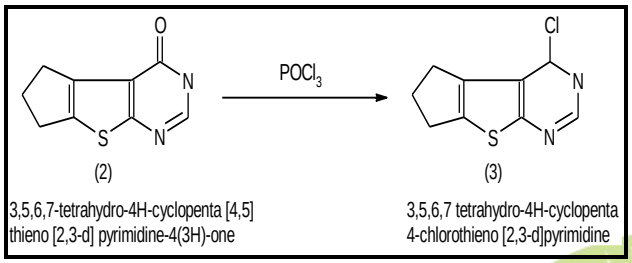
Scheme – 1

Synthesis of 3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-d]pyrimidin-4(3*H*)-one (Scheme 2): The compound (1) was heated with formamide (20 ml) in a round bottom flask in an oil bath at 60°C. The temperature was then gradually raised. The reaction mixture gets dissolved completely with the formation of brown solution at 110°C. The temperature of the oil bath was raised to 180-200°C, then the reaction mixture was heated at the temperature for 3 hrs. After the completion of the reaction, reaction mixture was allowed to cool at room temperature. The product separated as yellow needles was collected by filtration and washed with water several times and finally with 25 ml of acetone and then dried. The product was recrystallised from alcohol. Yield: 72%, melting point: 236°C.



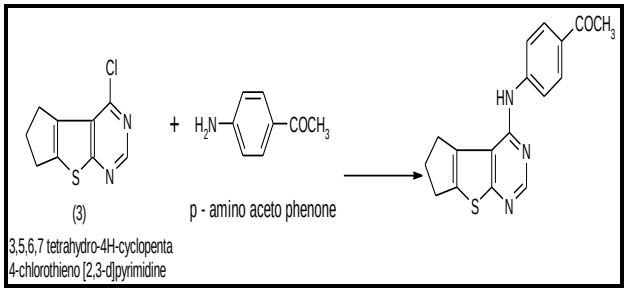
Scheme -2

Synthesis of 3, 5, 6, 7–tetrahydro-4*H*–cyclopenta [4, 5] 4-chloro thieno [2, 3-d] pyrimidine (Scheme 3): A mixture of compound 2 (0.01 mole) and 25 ml $POCl_3$ was refluxed for 8-10 hrs in round bottom flask. After completion of the reaction (monitored using TLC method) the excess of $POCl_3$ was removed by distillation, the resulting thick yellow liquid was poured over crushed ice, filtered washed with water and dried. The product was recrystallised from alcohol. Yield: 59%, melting point: 132°C.



Scheme-3

Synthesis of 1-[4-(6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-d]pyrimidin-4-yl-amino)phenyl] ethanone (Scheme 4): Compound 3 Equimolar concentration of p-amino acetophenone and 3-5 drops Conc. HCl was refluxed with alcohol in Round bottom flask for about 6hrs. After the reaction is complete (monitored by TLC) the mixture is poured over crushed ice. The solid formed was filtered off and residue is washed with 10% dilute ammonium hydroxide (NH_4OH). The product is recrystallised from alcohol. Yield: 67%, melting point: 214°C.



Scheme-4

Synthesis of 4-[4-(4-cholro cinnamoyl) phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine (Scheme 5a): phenyl hydrazine (0.11g, 0.001 mol) and compound 4 (0.35g, 0.001 mol) in absolute ethanol (20 ml) was heated in round bottom flask under reflux for 6 hrs. After cooling, the reaction mixture was poured onto ice, filtered and the precipitate was crystallized from $CHCl_3$/n-heptane. Yield: 58%, melting point: 218°C.

Synthesis of 4-[4-1-(phenyl hydrazone ethyl) phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine (Scheme 5b): 4-Chloro Benzaldehyde (Aromatic aldehyde) (0.001 mol) and solution of compound 4 (0.35g, 0.001 mol) in absolute alcohol (10ml) containing KOH (10%, 1 ml) was heated under reflux for 5 hours. The reaction mixture was then cooled, poured into ice cold water (20ml), filtered and the precipitate was crystallized from the Benzene or Petroleum Ether. Yield: 82%, melting point: 126°C.

Synthesis of 1-[4-(6,7-dihyro-5*H*-cyclopenta [4,5] thieno [2,3-d] pyrimidin-4-ylamino) phenyl)-2-(1*H*-indole-2-ylamino) ethanone (Scheme 5c): Compound 4 (0.001 mol) and 2-amino indole (0.001 mol) was refluxed with alcohol for about 10 hours then the reaction is completed, the reaction mixture was cooled and the poured on crushed ice. The solid found was filtered off, recrystallised from alcohol**.** Yield: 67%, melting point: 105°C.

Synthesis of 4-[3-(morpholine) phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine ethanone (Scheme 5d): Equimolar quantity of Compound 4 (0.01 mol) and 0.01 mol of morpholine are taken. To this mixture 5 mol of ethanol and 0.2 ml of try ethyl amine was added and refluxed for 5 hours. The reaction mixture was cooled and filtered, and then the compound obtained was dried and recrystallised using ethanol. Yield: 72%, melting point: 178°C.

Synthesis of 4-[3-(benzyl hydrazide) phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine ethanone (Scheme 5e): equimolar quantity of compound 4 (0.01 mol) and 0.01 mol of benzylhydrazide are taken in round bottom flask. To this mixture 20 ml of ethanol was added and refluxed on water bath for 8 hours. The excess solvent was removed by distillation. The solid crystals separated by

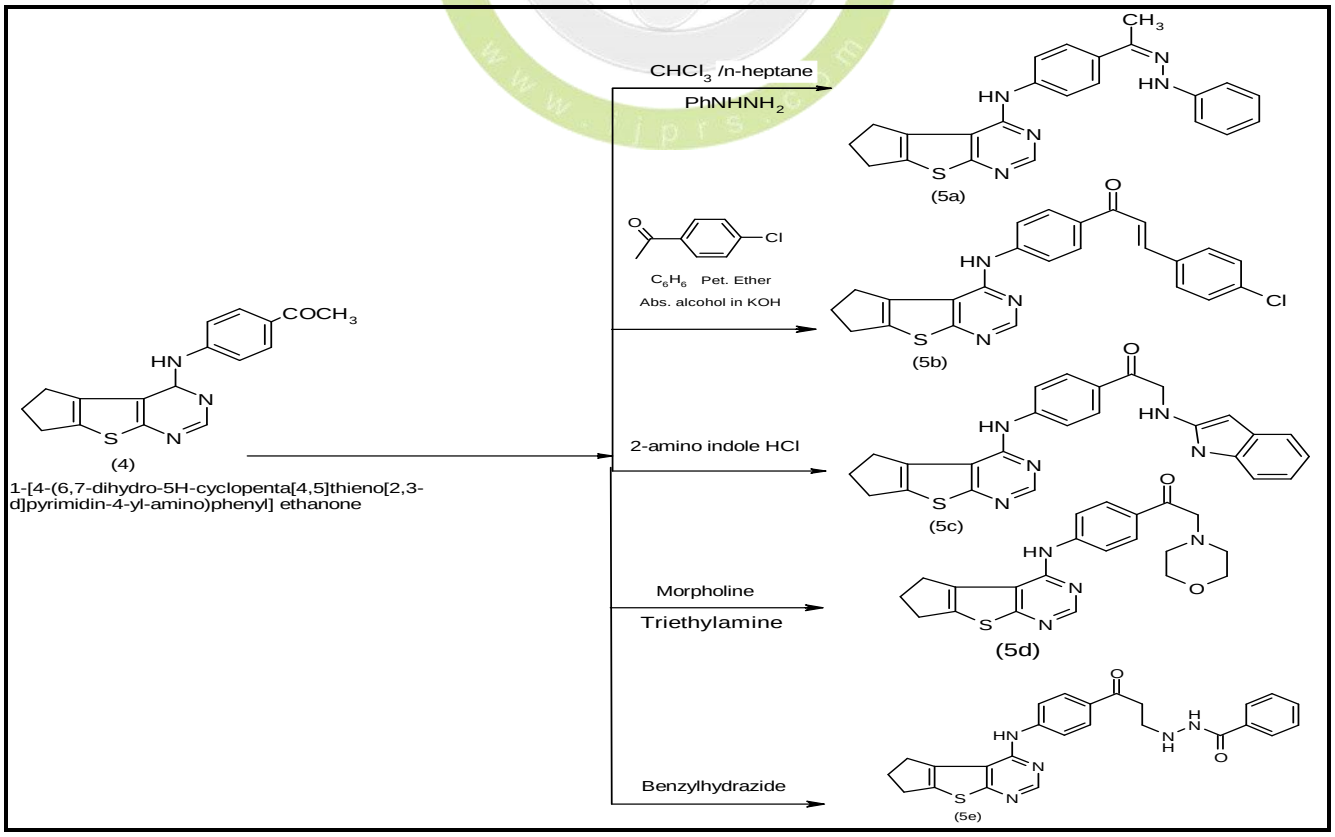
filtration were washed with cold water and recrystallised from ethanol. Yield: 60%, melting point: 121°C.

Compound [5a]: 4-[4-(4-cholro cinnamoyl) phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine. **^{1}HNMR [δ ppm]**: 8.39 (s, -CH-), 7.4 (d,-CH-), 7.01(s, -CH-), 7.0 (s, -NH-), 6.62 (s,-CH-), 6.5(s, -CH-), 6.46 (d, -CH-), 4.0 (d, -NH-), 2.55(d, -CH_2), 1.95(d, -CH_2), 0.9(s, -CH_3) **Mass (m/z):** 399 (100%, $C_{23}H_{21}N_5S$), 384 (C_2H_5), 373(C_2H_2), 323(C_6H_5), 348(C_4H_3), 372(HCN) Anal. Calcd for $C_{23}H_{21}N_5S$, % C, 69.15; H, 5.30; N, 17.53; S, 8.03. Found, %: C, 69.10; H, 5.32; N, 17.51; S, 8.01.

Compound [5b]: 4-[4-1-(phenyl hydrazone ethyl) phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine **^{1}HNMR [δ ppm]**: 8.39 (s, -CH), 7.56 (q, 4H), 6.65(d, 2H), 4.0(s, -NH-), 2.55(d, -CH_2), 1.95 (d, -CH_2) **Mass (m/z):** 431 (100%, $C_{24}H_{18}ClN_3OS$), 405(C_2H_2), 403(CO), 395(HCl), 355(C_6H_5), 380(C_4H_3), 404(HCN). Anal. Calcd for $C_{25}H_{21}N_5OS$, % C, 66.74; H, 4.20; Cl, 8.21; N, 9.73; O, 3.70; S, 7.42. Found, %: C, 66.72; H, 4.22; Cl, 8.20; N, 9.70; O, 3.71; S, 7.41.

Compound [5c]: 1-[4-(6,7-dihyro-5*H*-cyclopenta [4,5] thieno [2,3-d] pyrimidin-4-ylamino) phenyl)-2-(1*H*-indole-2-ylamino) ethanone **^{1}HNMR [δ ppm]**: 10.1 (s, -NH-,), 8.39 (s, -CH), 7.61(d, -CH), 7.4(s, -CH), 7.1(s, -CH), 6.57(d, -CH), 6.4(s, -CH), 4.32(d, -CH_2), 4.0(s, -NH), 2.55(d, -CH_2), 1.95(d, -CH_2) **Mass (m/z):** 439 (100%, $C_{25}H_{21}N_5OS$), 413(C_2H_2), 411(CO), 409(CH_2NH_2), 397(CH_2CO), 363(C_6H_5), 388(C_4H_3), 412(HCN). Anal. Calcd for $C_{25}H_{21}N_5OS$, % C, 68.32; H, 4.82; N, 15.93; O, 3.64; S, 7.30. Found, %: C 68.30; H, 4.81; N, 15.92; O, 3.62; S, 7.32

Compound [5d]: 4-[3-(morpholine) phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine. **^{1}HNMR [δ ppm]:** 8.39 (s, -CH), 7.61 (d, -CH), 6.57(d, -CH), 3.67(d, -CH_2), 3.62(d, -CH_2), 4.0 (s, -NH-), 2.55 (d, -CH_2), 2.37(d, -CH_2), 1.95(s, -CH_2) **Mass (m/z):** 394 (100%, $C_{21}H_{22}N_4O_2S$), 85(Mc Lafferty Product), 368(C_2H_2), 366(CO), 352(CH_2CO), 318(C_6H_5), 404(C_4H_3), 367(HCN). Anal. Calcd for $C_{21}H_{22}N_4O_2S$, % C, 63.94; H, 5.62; N, 14.20; O, 8.11; S, 8.13. Found, %: C, 63.92; H, 5.61; N, 14.21; O, 8.10; S, 8.12



Compound [5e]: 4-[3-(benzyl hydrazide) phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine **^{1}HNMR [δ ppm]**: 8.39 (s, -CH-,), 8.0 (s, -NH-), 7.95 (s, -CH), 7.61(s, -CH), 7.51(s, -CH), 7.44(s, -CH), 6.57 (s, -CH), 4.0(s, -NH), 3.91(d, -CH_2), 2.55(d, -CH_2), 2.0(s, -NH), 1.95(d, -CH_2) **Mass (m/z):** 458 (100%, $C_{24}H_{22}N_6O_2S$), 149((Mc Lafferty Product)), 432(C_2H_2), 430(CO), 42(CH_2NH_2), 416 (CH_2CO), 414 (CO_2), 414 ($OCNH_2$), 382(C_6H_5), 407(C_4H_3), 431(HCN). Anal. Calcd for $C_{24}H_{22}N_6O_2S$, % C, 62.86; H, 4.84; N, 18.33; O, 6.98; S, 6.99 Found, %: C, 62.84; H, 4.80; N, 18.29; O, 6.95; S, 6.95

RESULTS AND DISCUSSION

All the synthesized compounds were characterized on the base of their ^{1}H-NMR, Mass and basal or elemental analysis. The abstraction was aimed at evaluating the anti-inflammatory effect of compounds on mice.

Biological Activity

Anti-Inflammatory Activity [17]

Carrageenan induced Rat Paw Edema Method

Animals: Adult Wistar rats of both sexes weighing between 150-220 g were used for experiment. They were housed in accepted ecological conditions like, ambient temperature (250±10ºC), relative humidity (55±5%) and 12/12h light dark cycle. Animals had free access to standard pellet diet and water ad libitum. All animal experiments were carried out in accordance with the guidelines of CPCSEA. The institute animal ethical committee gave the approval for conducting animal experiments.

Procedure: Anti-inflammatory activity was assessed by the method described by (Winter et al., 1962). Albino rats of either sex weighing 150–220 g were divided in 3 groups. Group-1 received 0.5% CMC suspension (control), Group-2 accustomed accepted biologic Indomethacin (10 mg kg^{-1}, p.o) respectively. Group-3 received test compounds through the same route. Animals were treated with drugs by oral route and subsequently 1 h after treatment; 0.1ml of 1% suspension of carrageenan in normal saline was injected into the sub planter region of left hind paw to induce edema. The paw volume was again measured after the time interval of 2 hr and 4 hr after carrageenan injection using digital paw edema meter. The difference between the initial and subsequent values gave the actual edema volume which was compared with control. The inhibition of inflammation was calculated using the formula, % inhibition =100×(Vc-Vt/Vc), Where 'Vc' represents edema volume in control and 'Vt' edema volume in group treated with test compounds.

Statistical Analysis: Data analysis was carried out using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison tests. $P < 0.05$ was considered statistically significant.

Clinical study for anti-inflammatory activity of 4 [4-substituted phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine **(5a-5e)** revealed that the compound **5a** (Ar = 4-chloro cinnamoyl) and **5e** (Ar = benzyl hydrazide)) exhibited significant 50 % anti-inflammatory activity as compared to standard drug indomethacin after 2hr. All the compounds showed negligible activity after 4 hr.

Table 1: Anti-inflammatory activity of 4 [4-substituted phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine (5a-5e)

Compound	% age inhibition of rat paw edema (Dose= 10 $mgkg^{-1}$)	
	2hr	4hr
Indomethacin	64.70±0.03	72.40±0.04
5a	33.60±0.008**	18.63±0.02
5b	27.86±0.016*	14.50±0.01
5c	29.09±0.01**	10.76±0.01
5d	26.30±0.03	7.29±0.03
5e	31.10±0.01	14.00±0.02

*p<0.05, **p<0.01, ***p<0.001

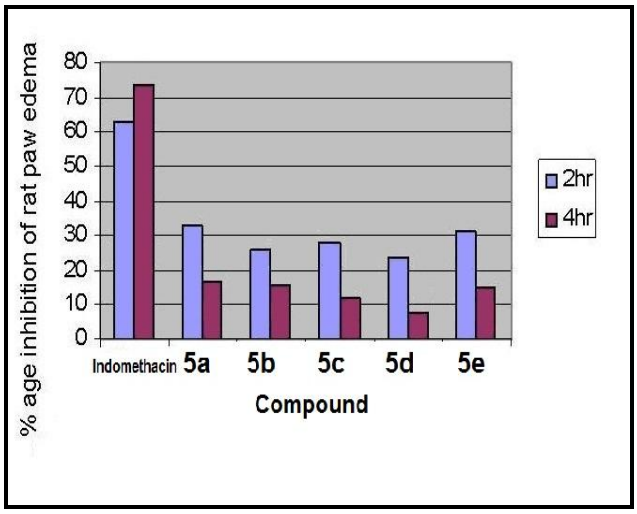


Figure 1: Anti-inflammatory activity of Anti-inflammatory activity of 4 [4-substituted phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine (5a-5e)

CONCLUSION

In conclusion, highly functionalized 4 [4-substituted phenyl amino] cyclopenta [4, 5] thieno [2, 3-d] pyrimidine **(5a-5e)** are synthesized from cyclopentanone. The anti-inflammatory activity is measured. In this study, the synthesized compounds may be used as lead compounds for anti-inflammatory activity and may further be evaluated for toxicological contour in approaching research.

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