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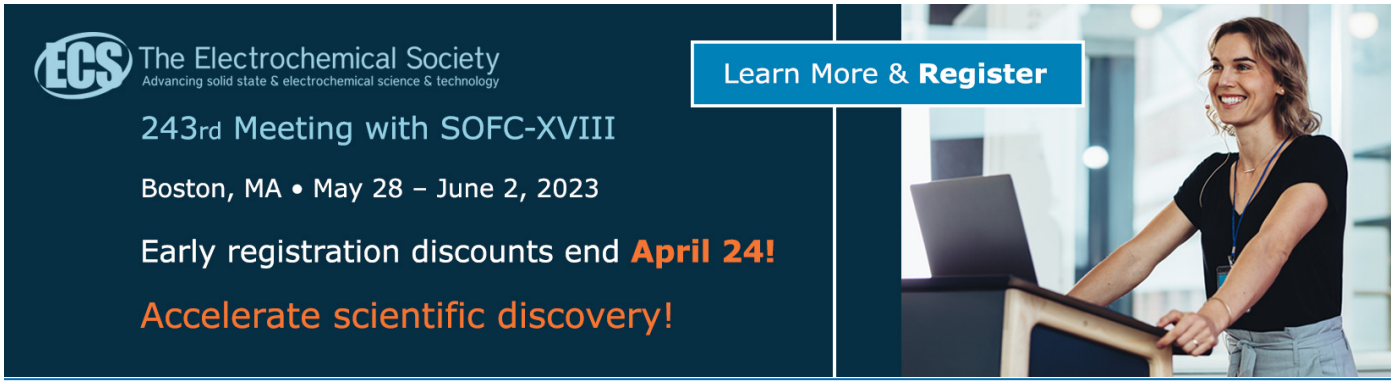

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Dimethylformamide-mediated synthesis and characterization of novel pyrazole- and pyrimidine-based 3,4-dihydropyrimidine-2(1*H*)-thione derivatives

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Abstract. Pyrimidine, an essential component of nucleic acid is currently reported for its potential application in Acquired Immune Deficiency Syndrome (AIDS) chemotherapy. Also, pyrazole nucleus, a versatile heterocyclic compound is gaining more attention in drug designs owing to its pharmacological therapeutic potentials. Hence, this present study deals with cost effective synthesis of 6-methyl-4-phenyl-5-(substituted-5-phenyl-4*H*-pyrazol-3-yl)-3,4-dihydropyrimidine-2(1*H*)-thione derivatives which are concisely known as pyrazole-based pyrimidine scaffolds. The multicomponent reaction of benzaldehyde, acetyl acetone and thiourea in the presence of catalytic amount of hydrochloric acid (HCl)*ab initio* produced 5-aceto-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine, **1**. Later, room temperature Claisen-Schmidt condensation of precursor **1** with diverse aromatic aldehydes which were benzaldehyde derivatives led to the formation of α,β-unsaturated carbonyl side chain, **2a-h**. Finally, the thermal annellation through synthetic cyclization furnished crude products which were purified by recrystallization to afford 6-methyl-4-phenyl-5-(substituted-5-phenyl-4*H*-pyrazol-3-yl)-3,4-dihydropyrimidine-2(1*H*)-thione derivatives 3a-h in a cheap condition. The chemical structures were authenticated using IR, UV, ^{1}H-NMR and ^{13}C-NMR as well as analytical data. The final products **3a-h** possessed good candidature for further investigation regarding their biological activities and pharmacological potential for new drug discovery.

1. INTRODUCTION

Heterocyclic compounds are cyclic organic compounds with one or more heteroatoms as part of the ring [1]. There is a considerable attention dedicated to the chemistry and biological potential of pyrimidine heterocycle owing to its uniqueness and peculiarity in drug domain [2]. Aside been the central component of nucleic acid (uracil, cytosine and thymine), pyrimidine also occurs naturally in substances such as vitamins like thiamine, riboflavin (found in milk, egg and liver), folic acid (from liver and yeast) and alkaloids obtained from tea, coffee and cocoa [2,3]. Pyrimidine which is much weaker that pyridine has been synthesized using various strategies. It has been documented to possess antimalarial [4], anticancer [5], antifungal[6,7], anticonvulsant [8]activities among others.

In a similar manner, pyrazolo[1,5-a]pyrimidine motifs derivatives are essential biomolecule in cancer treatment[5]. In addition, biological efficacy of pyrazole moieties in therapeutic medicine has been recently expounded in a review work by [9]while a research article demonstrated the microwave irradiated preparation of pyrazoline-linked template [10]. It is envisaged that incorporation of pyrazole into pyrimidine moieties as a linker will lead to noticeable boost of biological activities of such hybrid. Thus, it is highly commendable and synthetically conceivable to design and synthesize new pyrazole-

linked pyrimidin-2(1*H*)-thione motifs which might create window of opportunity for discovery of scaffold with greater dimension of efficacy for future drug development.

2. MATERIAL AND METHODS

2.1. Materials

Analytical grade reagents and solvents were used.All reagents and solvents were supplied by Sigma-Aldrich (USA) except hydrazine hydrate which was supplied by British Drug House (BDH, UK).Progress and product purity of the compounds synthesize was established on TLC plate. Melting point was carried out using Stuart point machine SMP10 (UK). Infrared data were generated with the Bruker FT-IR spectrophotometer(Germany)whereas the ultraviolet-visible analysis was obtained for the ethanolic solution of the synthesized compounds with the aid of Genesys^{TM} 10S UV-Vis. spectrophotometer (Thermo Scientific, USA). Both ^{1}H and ^{13}C nuclear magnetic resonance of the products were analyzed in DMSO-d_6 using Bruker NMR machine (Germany). The mass spectral data were generated using Waters GCT Premier Spectrometer manufactured by Waters Corporation, USA.Carlo Erba-1108 elemental analyzermanufactured in Germanywas used for C, H, N microanalysis.

2.2. Method

2.2.1. Preparation of 1-(4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) ethenone **1**

To a mixture of thiourea (13.14 mmol, 1.00 g), acetylacetone (13.14 mmol, 1.40 mL) and benzaldehyde (13.14 mmol,1.30 mL) was added ethanol (15.00 mL) and one drop of conc. HCl. The medium was refluxed for 4 h until the starting materials were totally consumed and there was noticeable evidence for the formation of product as envisaged. The reaction was monitored with TLC plate for this period to ascertain the product formation. The product formed 1-(4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) ethenone **1** (See Scheme 1) serves as precursor for the synthesis of chalcones **(2a-h)** when further reacted with various benzaldehyde derivatives (scheme 2).

2.2.2. Synthesis of **2a-h**: To a solution of NaOH (2.50 g) in 20 mL of water, 10 mL of ethanol was added with continuous stirring until it cooled to ambient condition. A mixture of appropriate ketone precursor **1** (14.15 mmol, 3.46 g) and benzaldehyde (14.15 mmol, 1.40 mL) drop-wisely to this solution with continuous stirring at room temperature for 2 h to afford **2a** (reaction completion was confirmed with TLC plate. The same procedure was repeated from other substituted benzaldehydes to afford **2b-h.**The compounds **2a-h** served as precursors for stage three.

2.2.3. General procedure for synthesis of pyrazol-incorporated pyrmidin-2(1H)-thione**3a-c.**

Precursor **2a-c** (6.21 mmol, 2.00 g) was reacted with hydrazine hydrate (6.21 mmol, 0.60 mL) in the presence of DMF and the reflux was done for 3 h with continuous stirring in the round bottom flask to afford **3a-c.** The product was monitored with TLC plate.

2.2.4. General procedure for synthesis of pyrimidone-incorporated pyrmidin-2(1H)-thione**3d-h**.

Chalcone **2d-h** (3.45 mmol, 1.30 g) was reacted with Urea (3.45 mmol, 0.25 g) in the presence of DMF and the reflux was done for 3 h with continuous stirring in the round bottom flask to afford **3d-h.** The confirmation of product formation was authenticated with thin layer chromatography.

Synthesis of (S)-6-methyl-4-phenyl-5-(5-phenyl-4*H*-pyrazol-3-yl)-3,4-dihydropyrimidine-2(1*H*)-thione, **3a** was obtained with percentage yield of 74.04%, melting point 163-165°C. R_f = 0.72, UV analyses, λ_{max} in nm (log ε_{max}): 217 (5.34), 250 (5.30). IR determination (KBr): 3425 (N-H), 3250 (N-H), 3050 (CH aromatic), 2952 (CH aliphatic), 2855 (CH aliphatic), 1600 (C=C), 1575 (C=N), 1370 (C-N), 755 (Ar-H) cm^{-1}. Mass spectral data (ESI): m/z (rel.%): 346.4 (M^+, 50%), 345.0 (M – 1, 1%), 283.3 (22%), 260.0 (M – CH_2CS – N_2, 99%), 255.2 (M – $PhCH_2$, 30%), 226.1 (25%), 209.1 (20%), 151.1 (M – 2Ph – CN_2H, 100%). ^{1}H-NMR (400 MHz, DMSO-d_6): 11.30 (s, 1H, NH), 7.95-7.93 (d, J = 8.08 Hz, 2H, Ph-H), 7.52-7.50 (d, J = 8.00 Hz, 2H, Ph-H), 7.37-7.33 (m, 3H, Ph-H), 7.25-7.20 7.37-7.33 (m, 3H, Ph-H), 6.45-6.44 (d, J = 5.40 Hz, 1H, NH-CH), 4.17-4.16 (d, J = 5.40 Hz, 1H, CH-NH), 2.32 (s, 2H, CH_3), 1.50 (s, 2H, CH_2). ^{13}C-NMR (100 MHz, DMSO-d_6): 170.1, 155.1, 153.7, 145.2 (2 × CH), 140.9, 137.3 (2 × CH), 128.6, 124.2, 122.8, 120.1 (2 × CH), 119.5, 115.3, 112.6, 110.3, 56.2 (CH), 31.3 (CH_2), 24.1 (CH_3) ppm.

Synthesis of (S)-5-(5-(2-chlorophenyl)-4*H*-pyrazol-3-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, **3b** was obtained with percentage yield of 64.24%, melting point 179°C. R_f = 0.79, UV analyses, λ_{max} in nm (log ε_{max}): 220 (5.40), 250 (5.31). IR determination (KBr): 3428 (N-H), 3255 (N-H), 2951 (CH aliphatic), 2854 (CH aliphatic), 1605 (C=C), 1557 (C=N), 1377 (C-N), 754 (Ar-H) cm^{-1}.

Synthesis of (S)-5-(5-(4-chlorophenyl)-4*H*-pyrazol-3-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione, **3c** was obtained with percentage yield of 66.69%, melting point 159-160°C. R_f = 0.75, UV analyses, λ_{max} in nm (log ε_{max}): 223 (5.40), 253 (5.28). IR determination (KBr): 3420 (N-H), 3254 (N-H), 2953 (CH aliphatic), 2856 (CH aliphatic), 1600 (C=C), 1570 (C=N), 1374 (C-N), 757 (Ar-H), 658 (C-Cl) cm^{-1}.

Synthesis of(S)-6'-methyl-6-(2-nitrophenyl)-4'-phenyl-2'-thioxo-1',2',3',4'-tetrahydro-[4,5'-bipyrimidin]-2(5*H*)-one, **3d** was obtained with percentage yield of 60.13%, melting point 70-71°C. R_f = 0.83, UV analyses, λmax in nm (log Ɛmax): λ_{max} in nm (log ε_{max}): 208 (5.28). IR determination (KBr): 3421 (N-H), 3253 (N-H), 3062 (CH aromatic), 2957 (CH aliphatic), 2852 (CH aliphatic), 1603 (C=C), 1575 (C=N), 1372 (C-N), 757 (Ar-H) cm^{-1}.

Synthesisof(S)-6-(4-methoxyphenyl)-6'-methyl-4'-phenyl-2'-thioxo-1',2',3',4'-tetrahydro-[4,5'-bipyrimidin]-2(5*H*)-one, **3e** was obtained with percentage yield of 69.34%, melting point 235-236°C. R_f = 0.73, UV analyses, λ_{max} in nm (log ε_{max}): 214 (5.24), 322 (5.45). IR determination (KBr): 3424 (N-H), 3255 (N-H), 3060 (CH aromatic), 2954 (CH aliphatic), 2850 (CH aliphatic), 1608 (C=C), 1575 (C=N), 1374 (C-N), 1320 (O-C), 750 (Ar-H) cm^{-1}

Synthesis of (S)-6-(4-ethoxyphenyl)-6'-methyl-4'-phenyl-2'-thioxo-1',2',3',4'-tetrahydro-[4,5'-bipyrimidin]-2(5*H*)-one, **3f** was obtained with percentage yield of 68.13%, melting point 228°C. R_f = 0.71, UV analyses, λ_{max} in nm (log ε_{max}): 211 (5.04), 325 (5.15). IR determination (KBr): 3421 (N-H), 3248 (N-H), 2950 (CH aliphatic), 2853 (CH aliphatic), 1600 (C=C), 1574 (C=N), 1371 (C-N), 1323 (O-C), 752 (Ar-H) cm^{-1}

Synthesis of (S)-6-(4-hydroxyphenyl)-6'-methyl-4'-phenyl-2'-thioxo-1',2',3',4'-tetrahydro-[4,5'-bipyrimidin]-2(5*H*)-one, **3g** was obtained with percentage yield of 81.00%, melting point 231°C. R_f = 0.73, UV analyses, λ_{max} in nm (log ε_{max}): 214 (5.98), 322 (5.29), 418 (2.95), 457 (2.90). IR

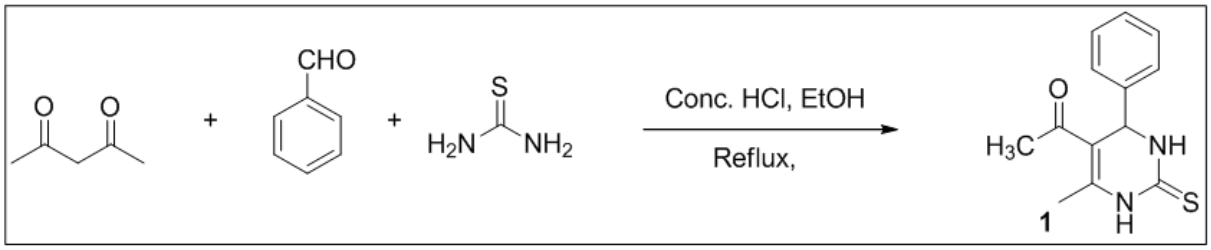
determination (KBr): 3511 (OH), 3363 (N-H), 3278 (N-H), 3119 (CH aromatic), 2954 (CH aliphatic), 2854 (CH aliphatic), 1647 (C=C), 1571 (C=N), 1379 (C-N), 1316 (O-C), 795 (Ar-H) cm^{-1}

Synthesis of (S)-6-(4-hydroxy-3-methoxyphenyl)-6'-methyl-4'-phenyl-2'-thioxo-1',2',3',4'-tetrahydro-[4,5'-bipyrimidin]-2(5*H*)-one, **3h** was obtained with percentage yield of 61.10%, melting point 196°C. R_f = 0.71, UV analyses, λ_{max} in nm (log ε_{max}): 208 (4.48), 322 (4.48), 607 (2.08), 535 (2.08). IR determination (KBr): 3510 (OH), 3365 (N-H), 3276 (N-H), 3050 (CH aromatic), 2959 (CH aliphatic), 2851 (CH aliphatic), 1622 (C=C), 1575 (C=N), 1378 (C-N), 1320 (O-C), 755 (Ar-H) cm^{-1}

3. RESULTS AND DISCUSSION

Pyrimidine and pyrazole are heterocyclic compounds with well-known and highly valuable benefits in medicinal chemistry research. Thus, in this study we aimed at strategic preparation of pyrimidine-inserted compounds with pyrazole inclusion and incorporation because it was envisaged that this might lead to enhancement of bioactivity of the resulting targeted motifs. The cost-effective synthesis using cheap and readily available starting material was carried out in three stages to afford the titled compounds as envisaged. First and foremost, multi-component reaction MCR strategic synthesis of pyrimidin-2(1*H*)-thione**1** was achieved from the acid catalyzed reaction of acetylacetone, benzaldehyde and thiourea in absolute ethanol via conventional heating method. Acetyl side chain of precursor **1** was then converted to enolate anion allowed to undergo Claisen condensation with aromatic aldehydes **a-h** to furnish α.β-unsaturated carbonyl compound chalcone **2a-h** (Scheme 2) in good to excellent yields ranging from 67 to 91%. The product was achieved at ambient temperature. The earlier part of last stage of the reaction endeavor herein involved the reductive cyclization of the intermediate chalcone **2a-c** with hydrazine hydrate in an ecofriendly manner to furnish the final products pyrazole-incorporated pyrimidin-2(1*H*)-thione motifs **3a-c**. The latter part of the last stage dealt with thermal annelation of the chalcones **2d-h** with urea to access pyrimidone-incorporated pyrimidin-2(1*H*)-thione motifs **3d-h** (Scheme 3). The result of the physicochemical properties according to Table 1, showed that the molecular weight was consistent with the expected based on the elemental analysis and the product colour were basically two. Compounds **3a, 3c, 3d, 3e, 3f** and **3h** were yellow and at the rest had brown coloration. The $R_f$values ranging from 0.70 for **3h** to 0.83 for **3d** were obtained as the from the were obtained as the ranges of the Rf using DCM/MeOH (9.5:0.5). as the eluent. The melting points varied from 70-71^{o}C for 3d to 235-236^{o}C for **3e**. Although, all the compounds had improved and encouraging yields, the 3g had the highest yield (81%) while **3d** had the lowest yield (60%).

In the IR analysis, the stretching vibrational frequencies that were general to compounds **3a-h** found at 3428-3248 cm^{-1}, 3119-3050 cm^{-1}, 2959-2850 cm^{-1}, 1647-1600 cm-1 and 1575-1557 cm^{-1} depicted the presence of N-H, C-H aromatic, C-H aliphatic, C=C, and C=N respectively. Specific O-H broad bands of compounds **3g** and **3h** were found to absorb at 3511-3510 cm^{-1}. According to the result of uv-visible spectroscopic analysis the wavelength values at 208-223 nm was due to the presence of benzene nucleus while the bathochromic shifts noticeable at other peak above 230 nm were due to the presence of auxochrome and additional conjugation from extra C=C and tendency for delocalization of non-bonding electron inform of $n\rightarrow\pi^*$ electronic transition [10]. The result of the mass spectral data of compound **3a** (Fig. 1) showed that the molecular ion peak was 346.4401 which was in agreement with the molecular mass (346.45) of compound **3a.** The base peak was observed at m/z 151 which depicted the loss of 2 molecules of phenyl and CN_2H group. Other fragmentation patterns led to the formation of daughter ions at m/z of 283.3, 260.0, 226 and 209.1 with the intensities of 22%, 99%, 25% and 20% respectively. The m/z of 260.0 was accounted for via the loss of $CH_2CS + N_2$

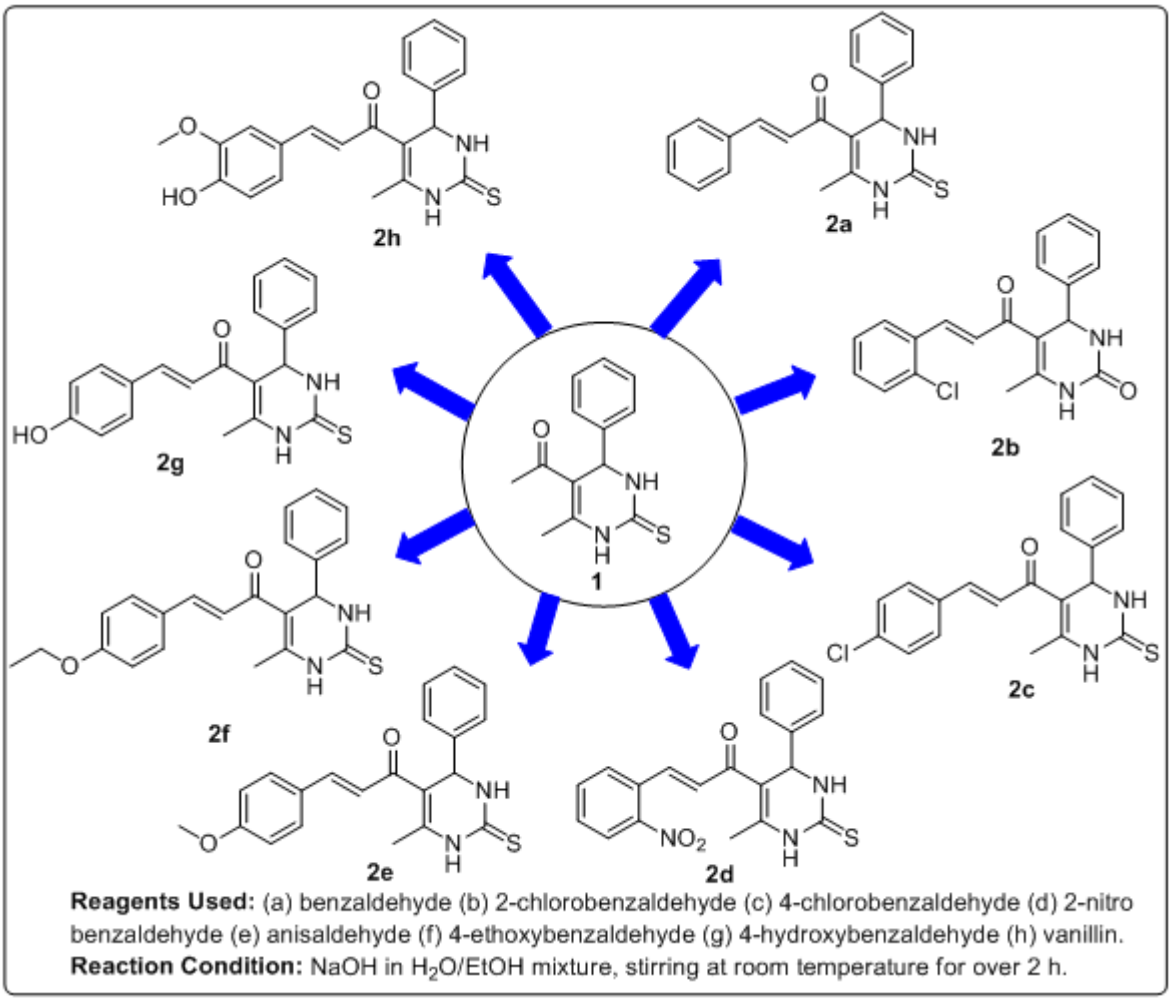


Scheme 1: MCR synthesis of 1-(4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethenone, **1**

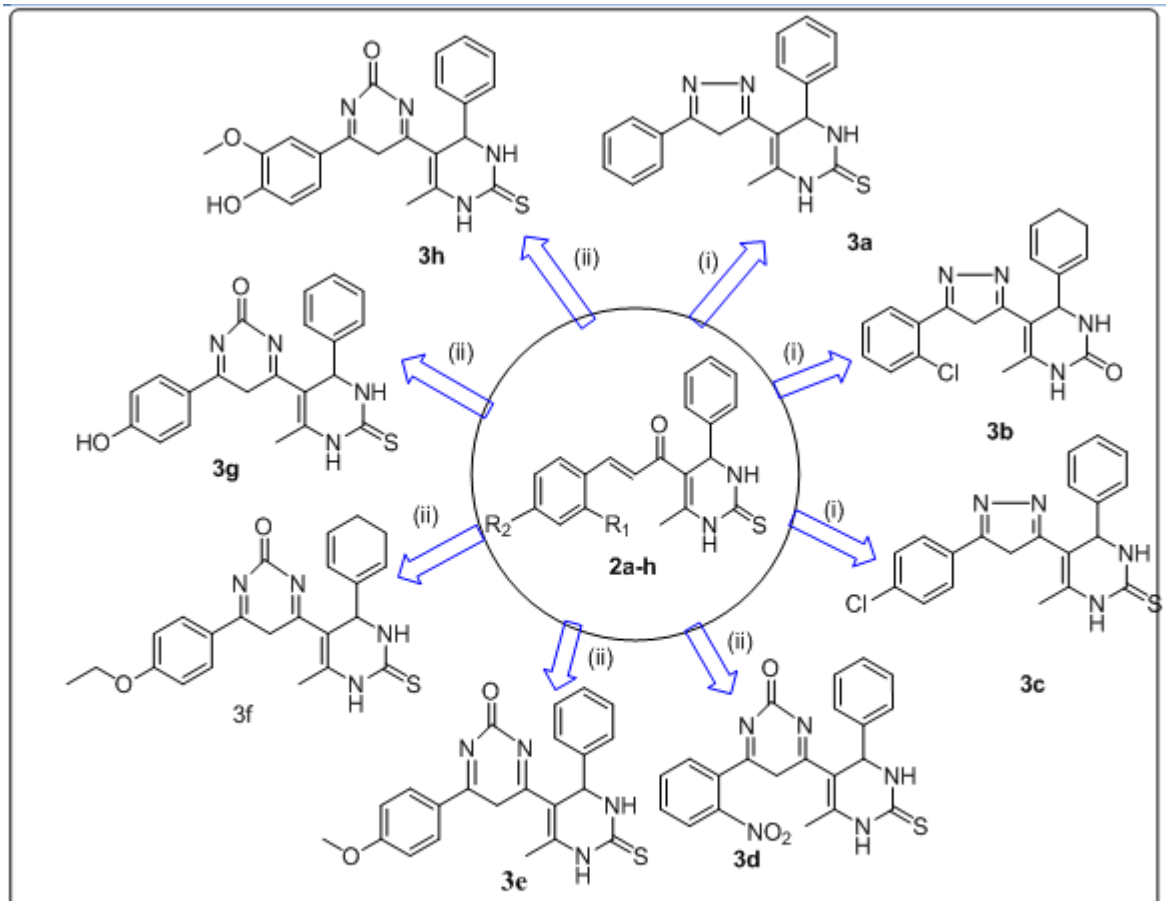
Table 1: Physicochemical properties of the synthesized pyrimidin-2-thione derivatives**3a-h**

Comp No	MolecularFormula (Molecular Weight)	Colour	R_f Value	Melting point/ °C	Yield %	Elemental analysis: %Calcd. (%Found) C	H	N
3a	$C_{20}H_{18}N_4S$ (346.45)	Yellow	0.72y	162 (s)	74.04	69.34(69.46)	5.24(5.09)	16.17(16.33)
3b	$C_{20}H_{17}NClN_4S$ (380.89)	Brown	0.79y	179 (s)	64.24	63.07(62.88)	4.50(4.75)	14.70(14.82)
3c	$C_{20}H_{17}NClN_4S$ (380.89)	Yellow	0.75y	159-160	66.69	63.07(62.91)	4.50(4.43)	14.71(14.90)
3d	$C_{21}H_{17}N_5O_3S$ (419.46)	Brown	0.83y	70-71	60.13	60.13(59.92)	4.09(3.84)	16.70(16.57)
3e	$C_{22}H_{20}N_4O_2S$ (404.48)	Yellow	0.73y	235-236	69.34	65.33(65.58)	4.98(5.11)	13.85(14.08)
3f	$C_{23}H_{22}N_4O_2S$ (418.51)	Yellow	0.71y	228 (s)	68.31	66.01(65.87)	5.30(5.55)	13.39(13.58)
3g	$C_{21}H_{18}N_4O_2S$ (390.46)	Brown	0.73y	231 (s)	81.00	64.60(64.74)	4.65(4.84)	14.35(14.54)
3h	$C_{22}H_{20}N_4O_3S$ (420.48)	Yellow	0.70y	196 (s)	64.10	62.84(63.03)	4.79(5.01)	13.32(13.51)

y = DCM/MeOH (9.5:0.5). Comp No = Compound Number. S = sharp melting point.



Scheme 2: Synthetic Route to α,β-Unsaturated Carbonyl (Chalcones, **2a-h**)



Reagents Used:(i) Hydrazine hydrate. (ii) Urea. **Reaction Condition:** DMF; Reflux for 3 h.

	3a	3b	3c	3d	3e	3f	3g	3h
R_1	H	Cl	H	NO_2	H	H	H	H
R_2	H	H	Cl	H	CH_3O	C_2H_5O	OH	OH,OCH_3

Scheme 3: Synthesis of Pyrazole-and Pyrimidinone-based Pyrimidin-2-thione Derivatives **3a-h**

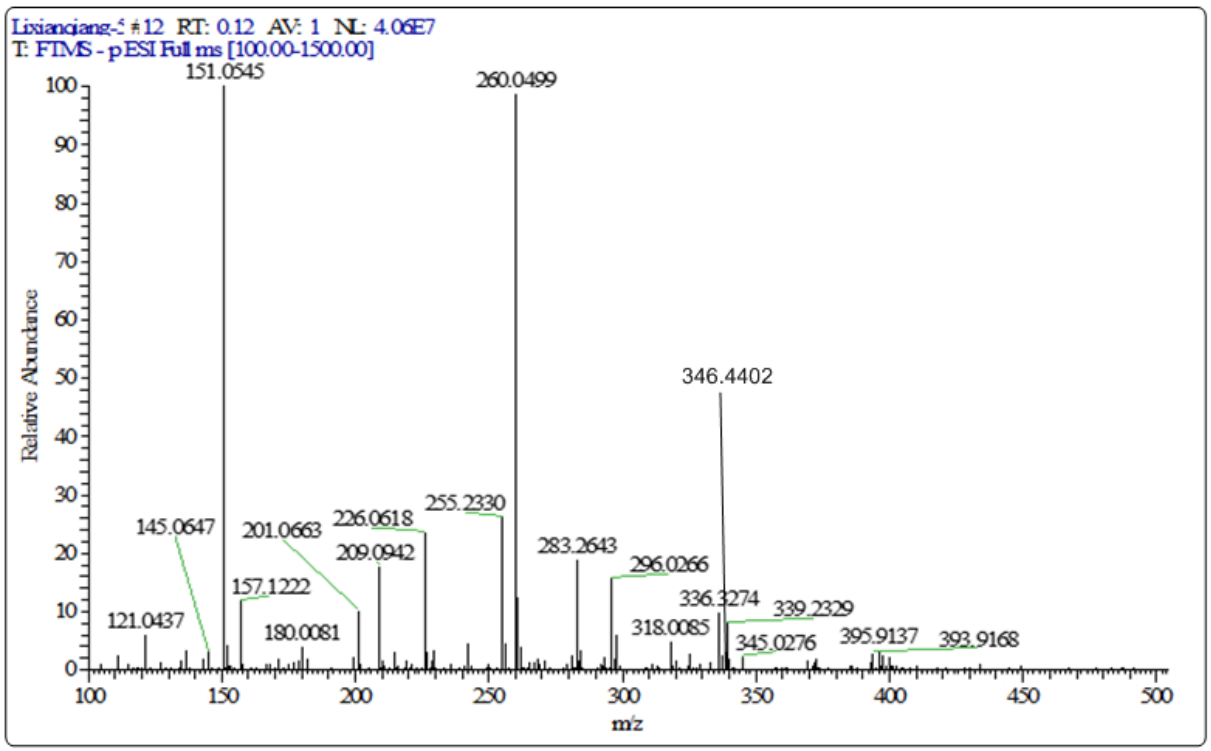


Fig. 1: Mass Spectral Data of Compound3a

4. CONCLUSION

In the noteworthy that a cost-effective synthesis of pyrazole-incorporated pyrimidin-2(1*H*)-thione**3a-h** was achieved herein in excellent yield using multicomponent reaction (MCR) strategy. The structural elucidation was established through physicochemical method and spectroscopic means after purification of the crude products. Thus, the pyrimidinones library synthesized herein could stand the chance of being considered for further investigation of their biological and pharmacological activities for future drug development.

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