Solvent free Montmorillonite K-10 Clay catalyzed synthesis and Structure elucidation of pyrazoloimidazole-2-thione Derivatives

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Abstract

The pharmaceutical industry faces challenges such as the use of toxic solvents, excessive use of energy, waste generation and the implementation of conventional procedures that do not adhere to green chemistry principles. In the present study, we report the prompt mineral (Montmorillonite K-10 clay) triggered cyclo-condensation of chloroacetic acid with arylthiourea subsequently followed by Knoevenagel condensation with aromatic aldehyde in combination with sodium acetate without solvents microwave irradiation results in 3-aryl-5-benzylideno-2-thiohydantoins 4(a-l).

The substances 4 (a-l) with hydrazine hydrate in glacial acetic acid offered the intermediate acetyl hydrazone of 4(a-l) which on cyclo-isomerization under reaction conditions gave 1,8-diaryl-4,8-dihydro-1-acetylpyrazolo[3,4-c] imidazole-2-thiones 5 (a-l).

Keywords: Green chemistry, Heterogeneous catalysis, Knoevenagel condensation, Montmorillonite K-10 clay, Microwave-irradiation, Pyrazoloimidazol-2-thione, Solvent-free.

Introduction

The widespread use of hazardous solvents in pharmaceutical manufacturing poses a significant risk to human health and the environment. However, in the last few years, sustainable chemistry has impacted the healthcare industry's processes by reducing the use of traditional chemical solvents[6], reducing waste generation by using recyclable materials and adopting environmentally friendly organic synthetic procedures.

The use of microwaves (MW) in solvent-free processes[20,30]. has been especially important for manufacturing. MW irradiation accelerates chemical reactions, highlighting its potential for innovative processes. This improvement is especially noticeable in heterogeneous catalytic systems when compared with conventional heating under identical temperature conditions, due to interaction(s) between the MW radiation field and the catalyst itself. For the above reasons, it has given rise, over the years, to a strong interest in the field of synthesis[14,18,39].

In recent decades, heterogeneity of catalysts has gained popularity in eco-sustainable organic chemical manufacturing because of their greater activity than homogeneous catalysts[19,68]. The pharmaceutical sector is preferred due to its ease of recovery, stability and capacity to reduce waste. Lewis acid heterogeneous catalyst formation from waste materials has become more common recently[28,46,51]. For example, sulfonic acid-functionalized active carbon (AC) prepared from developed tea leaves has been investigated for the synthesis of 2-substituted benzimidazole and benzothiazole[57].

Consuming volatile hazardous solvents in the chemical sector poses a risk to human health and the environment.[56] Therefore, the need for clean processes that reduce energy consumption, waste and expenditure is an ongoing issue. Various studies have advocated the use of novel techniques like "green" chemicals[24], mainly water[43,44,48], ionic fluids[1], deeply eutectic solvents[2] and biological solvents[27,37,52]. However, solvent-free conditions[33,45,47] are the most effective options for conducting eco-sustainable chemical processes. Reactions free of solvents can be performed by employing reactants either alone or by including them in solid bases simplifying the testing procedures while significantly reducing the negative environmental effects.

The use of microwave energy has been proposed as a useful method for increasing the speed of reactions, simplifying processes and enhancing yields in chemical reactions free of solvents triggered by solid Lewis acids[11,17,34,49]. Solid supports have become popular in organic compound production owing to their highly adaptable properties, thermal resistance and inexpensive cost. Undoubtedly, experimental methods that depend on solid-state processes will minimize pollution. Solid supports (clays, permutit, silica, alumina, or other matrix structures) are commonly used in reactions to improve yields, to increase reaction speed and to minimize environmental impact[24,63].

Solid Lewis acid catalysts are commonly used in this scenario and the use of heat[41] can drive reactions. Montmorillonite K-10 clay, known to act both as protic and Bronsted acid, is an extensively investigated catalyst found useful for numerous organic reactions such as the production of g-lactones[61], fused heterocycles[15], Friedel Crafts reaction[66], biomarkers, oxidative demethylation of methyl phenols to benzoquinones[7], internal cyclization, Michael addition[55], Boc group removal from aromatic amines[64],

Diels Alder reaction[5] and so on. Montmorillonite is used in numerous microwave reactions, both in liquid form and in the absence of a solvent[9,12]. Essential pharmaceuticals frequently contain heterocyclic molecules as constituents[20].

The widespread use of heterocyclic molecules in the pharmaceutical sector can be attributed to the availability of a diverse range of reactions that allow for subtle structural changes in heterocyclic materials[25,40]. The processes were carried out in the absence of a solvent under microwave exposure with montmorillonite K-10 as the solid catalyst.

The methodology's novelty stems from its environmentally friendly operation, formation of structurally distinct molecules, quick reaction time and high yield.

Montmorillonite is a diverse and eco-sustainable catalyst due to its inexpensive price, simple care, simple extraction via a filtering method and potential for use without solvents in microwave ovens or during ultrasound exposure[38]. Montmorillonite, like others, is extensively available and possesses a high surface area that contains Brønsted and Lewis acid sites that catalyse organic reactions[11,16,37,40,50]. Recently, an easy and sustainable protocol to produce novel substituted 2-aryl benzimidazoles was established using $ZrOCl_2 \cdot nH_2O$ supported on montmorillonite K10[60].

Substances with imidazole frameworks are currently attracting consideration for their medicinal properties[14,26]. The most significant of these include 2-thioxoimidazolidinones, which have antiviral properties, especially against HIV[42,59]. Pyrazole compounds have numerous medical and biological applications including cancer-fighting, anti-inflammatory, fungicidal, antimicrobial, anti-insecticidal, analgesic, antiviral, anticonvulsant, antidiabetic, antipyretic, anti-arrhythmic, anti-depressant, anti-hyperglycaemic, anti-oxidative and herbicidal[4,8,17,53]. Phenazone was the initial pyrazole available in the market as an antipyretic agent[67]. The medicinal value of pyrazole can be analysed using lists of readily accessible drugs such as Celecoxib[3], Lonazolac[50], Mepirizole[54], Rimonabant[65], Accomplia[32], Cimetidine[31], Fipronil, Deracoxib[23] etc.

The investigation of the effect of structure on activity revealed that by combining one heterocyclic moiety with another, the therapeutic profile is typically improved many times that that of any individual heterocyclic moiety. Multiple imidazole-2-thione variants have received considerable attention owing to their broad medicinal qualities and biological functions[22,62]. Using molecular diversity techniques to identify drugs involves multiple disciplines including computerized chemistry, organic chemical synthesis and molecular biology.

The primary goal of the work stated here is to deliver an account of one aspect of molecule diversity-based drug search, namely the establishment of a general synthetic approach to the production of heterocyclic counterparts for screening lead molecules for unique assays in the archives of chemicals amassed through organic synthesis. The use of mineral-supported reagents and microwave irradiation in solvent-free conditions is an extensively documented environmentally friendly protocol with chemical and biological applications[13,58].

Material and Methods

Each experiment was performed using a laboratory microwave oven (Model BP 310/50) with an electrical output of 600 W and an operating frequency of 2450 MHz. All chemicals used in this investigation were of analytical reagent grade. Melting points were obtained using the open-glass capillary technique and were not corrected. Each chemical was used exactly as received. The reaction results were tracked using TLC (Merk silica gel). The IR spectra were captured using a Shimadzu FTIR-420 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 400°C using a Bruker AVANCE DPX (400 MHz) FT spectrometer in $CDCl_3$ with TMS as an internal standard (chemical shift in δ, ppm). Mass spectral data were recorded on a JEOL SX- 303 (FAB) mass spectrophotometer at 70ev. The elements were examined using a Coleman automatic C, H and N analyzer.

Thermal Method: Montmorillonite K-10 clay (0.50 g) was placed in a solution containing aryl thiourea 1 (0.02 mol), chloroacetic acid 2 (0.002 mol), aryl aldehyde 3 (0.02 mol) and sodium chloroacetate (0.001 mol) in DMF (100 mL) while stirring and the resultant mixture was heated on a thermostatic oil bath at 90°C for the time specified in table 1. The reaction development was tracked using TLC (Hexane: MeOH; 6:4 v/v). Once the reaction was completed, the resultant mixture was allowed to cool, put into water and filtered and the product was retrieved with ethanol (3x50 mL). The resulting extract was dried under low pressure to produce a product that was then crystallized from ethanol to yield analytically pure compounds (4_{a-l}).

Microwave irradiation Method: Montmorillonite K-10 clay (0.50g) was thoroughly mixed with a mixture of arylthiourea 1 (0.02mol), chloroacetic acid 2 (0.02mol), aromatic aldehyde 3 (0.02mol) and sodium acetate (0.002mol) in DMF (20ml) before the solvent was dried out under low pressure. The samples were placed in a 40 ml vial and heated in a microwave at 600 W for 2-3 minutes. The reaction mixture was mixed well outside the microwave oven for 2 min before being irradiated for an additional 3-4 minutes. This irradiation-mixing process was continued for all compounds at the specific times listed in table 1. The end of the reaction was determined by TLC (Hexane: MeOH, 6:4 v/v) and the product was separated with ethanol (3x8 mL). The extract was filtered and the filtrate was removed under low pressure to obtain the final product. The final product was recrystallized from ethanol to obtain analytically pure compounds (4_{a-l}).

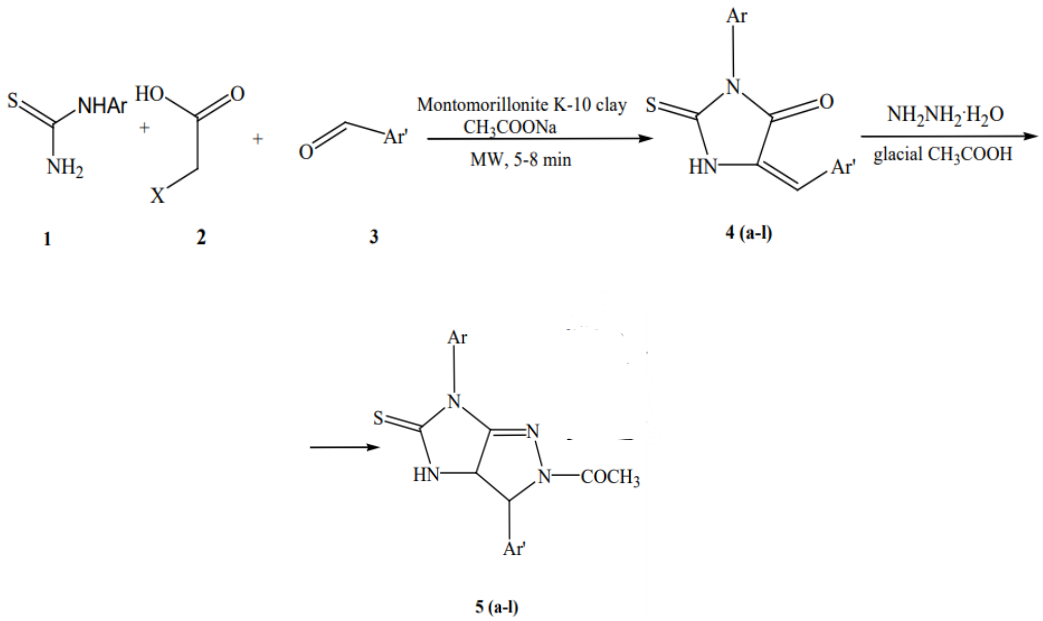
1,8-Diaryl-4,8-dihydro-1-acetylpyrazolo[3,4-c] imidazol-2-thione (5_{a-l}): A solution of aryl-5-benzylideno-2-thioxohydantoin $4_{(a-l)}$ (0.002 mol), hydrazine hydrate (0.2 mol) and glacial acetic acid (1 mL) was vigorously stirred at ambient temperature for 3-5 hours. The resulting solid was

separated and processed with water to yield compounds 5_{a-l}. Subsequently, they were cleaned and purified by recrystallization from water-based ethanol.

Results and Discussion

Montmorillonite K-10clay (K-10clay) catalysed the cyclo-condensation of arylthiourea 1 with chloroacetic acid 2 under free solvent microwave radiation, yielding 3-aryl-2-thioxoimidazolidin-4-one (Scheme 1). 3-aryl-2-thioxoimidazolidin-4-one upon Knoevenagel condensation with an aromatic aldehyde in the presence of CH_3COONa, gave 3-aryl-5-benzylideno-2-thiohydanto. Regioselectivity in the cyclo-condensation of aryl thiourea with chloroacetic acid was attributed to differences in nucleophilicity between the $-NH_2$ and -NHAr groups.

Additional delocalization of electrons on the aromatic ring of –NHAr makes it a poor nucleophile and hence, the $–NH_2$ group by nucleophilic substitution of α-halogen of $ClCH_2COOH$ resulted in an intermediate that was cyclized to produce $4_{(a-l)}$.



Scheme 1

Table 1
Physical Data of 3-Aryl-5-benzylideno-2-thioxohydantoin (4_{a-l})

Compd	Ar	Ar'	Time		Yield		M.P.
			MWI (min)	Thermal (hour)	MIW (min)	Thermal (hour)	
4a	C_6H_5	C_6H_5	**5**	4	85	35	220
4b	C_6H_5	4-Cl-C_6H_4	**6**	5	82	34	235
4c	C_6H_5	4-HO-C_6H_4	**6**	3	87	36	145
4d	C_6H_5	4-MeO- C_6H_4	**5**	3	90	37	215
4e	C_6H_5	2-NO_2- C_6H_4	**7**	5	84	32	250
4f	C_6H_5	3-MeO, 4-HO- C_6H_3	5	3	87	34	195
4g	4-Me-C_6H_4	C_6H_5	6	4	82	31	230
4h	4-Me-C_6H_4	4-Cl-C_6H_4	7	6	83	33	248
4i	4-Me-C_6H_4	4-HO- C_6H_4	6	4	86	33	180
4j	4-Me-C_6H_4	4-MeO- C_6H_4	6	4	87	34	220
4k	4-Me-C_6H_4	2-NO_2- C_6H_4	5	5	88	33	185
4l	4-Me-C_6H_4	3-MeO, 4-HO-C_6H_3	5	4	88	35	200

Other mineral supports, viz. silica gel, neutral, or basic alumina, were far less effective, resulting in either no reaction (in the case of basic alumina) or relatively very low yields (15-30%) of $4_{(a-l)}$ (in the case of silica gel and neutral alumina). To compare the final temperature, the temperature was measured by immersing a glass thermometer into the reaction mixture immediately after MW irradiation and was found to be <88°C. The reactions were also carried out using a thermostatic oil bath at the same temperature (88°C) as in the MW-activated method but for a longer period (Table 1).

It was found that the MW method significantly improved the yield. MW enhancement of yields and reduction in reaction time can be rationalized based on the formation of dipolar activated complex I from uncharged reactants complex II from uncharged adduct in these reactions and greater stabilization of the more dipolar activated complex by dipole-dipole interaction with electric field of the microwaves as compared to the less dihydro-1-acetylpyrazolo[3,4- c]imidazol-2-thiones (Scheme 1) in 75-88% yields (Table 2).

^{1}H NMR and IR Spectra: Spectral analysis using ^{1}H NMR and IR confirmed the structure of 4_{a-l} (Table 3). The formation of compounds 4a-l confirmed by signals at δ 7.2 - 7.4 as multiplets for aromatic protons, δ 4.80 as singlet for the vinylic proton of the benzylideno group and δ 2.1 - 2.5 as singlet for –NH- proton in ^{1}H NMR spectra. Absorption spectrum bands in the region of 3300-3350 cm^{-1} for N-H, 3050 cm^{-1} for aromatic C-H, 1690 cm-1 for C=O, 1620 cm-1 for C=C, 1600,1500, 1468 cm-1 for aromatic C-C, 1200 cm-1 for C=S and 1180 cm-1 for C-N stretching in IR spectra and 1200 cm-1 for C-N stretching in 1H NMR spectra were suggestive of the synthesis of compounds 4_{a-l}. Spectral and element investigations also validated the structure of 5_{a-l} (Table 4). All the produced compounds' spectra closely resembled the fused pyrazole moiety's 2-thioxoimidazolidine ring.

Table 2
Physical Data of and 1,8-Diaryl-4,8-dihydro-1-Acetyl pyrazolo[3,4-c] imidazol-2-thione (5_{a-l})

Compd.	Ar	Ar'	Yield (%)	M.P. (°C)
5a	C_6H_5	C_6H_5	80	112
5b	C_6H_5	4-Cl-C_6H_4	82	122
5c	C_6H_5	4-HO-C_6H_4	84	124
5d	C_6H_5	4-MeO- C_6H_4	86	119
5e	C_6H_5	2-NO_2- C_6H_4	77	115
5f	C_6H_5	3-MeO, 4-HO-C_6H_3	90	130
5g	4-Me-C_6H_4	C_6H_5	84	110
5h	4-Me-C_6H_4	4-Cl-C_6H_4	88	118
5i	4-Me-C_6H_4	4-HO- C_6H_4	90	123
5j	4-Me-C_6H_4	4-MeO- C_6H_4	91	126
5k	4-Me-C_6H_4	2-NO_2- C_6H_4	87	128
5l	4-Me-C_6H_4	3-MeO, 4-HO-C_6H_3	90	132

Table 3
Spectral Characterization Data of 3-Aryl-5-benzylideno-2-thioxohydantoin (4a-l)

Compd.	Mol. Formula	IR (KBr, υ cm^{-1})	^{1}H NMR spectroscopy (400 MHz, $CDCl_3$, δ, ppm)	MS (EI, *m/z* (M^+)
4a	$C_{16}H_{12}N_2OS$	3320, 3050, 1690, 1620, 1600, 1500, 1468, 1200 and 1180	δ 2.1 (s, 1H, -NH-), 4.8 (s, 1H, -C=CHAr), 7.2-7.4 (m, 10 H, Ar-H)	280 (M^+)
4b	$C_{16}H_{11}NOSCl$	3330, 3052, 1695, 1620, 1600, 1500, 1460, 1210 and 1190	δ 2.4 (s, 1H, -NH-), 5.2 (s, 1H,-C=CHAr), 7.21-7.51 (m, 9H, Ar-H)	314.5(M^+)
4c	$C_{16}H_{12}N_2O_2S$	3320, 3050, 2530, 1685, 1618,1600, 1502, 1469,	δ 2.2 (s, 1H, -NH-), 4.4 (s,1H, -OH exchangeable with D_2O), 4.78 (s, 1H, -C=CHAr), 6.9-7.4 (m, 9H, Ar-H)	296.12(M^+)
4d	$C_{17}H_{14}N_2O_2S$	3320, 3050, 2530, 1690, 1620,1600, 1500, 1468,1200, 1180 and 1120	δ 2.3 (s, 1H, -NH-), 3.3 (s, 3H, -OCH_3), 4.82 (s, 1H, -C=CHAr), 7.07-7.76 (m, 9H, Ar-H)	310(M^+)
4e	$C_{16}H_{11}N_3O_3S$	3330, 3045, 1690 1625, 1600, 1504, 1470, 1210 and 1190	δ 2.5 (s, 1H, -NH-), 4. 2 (s, 1H, -C=CHAr), 6.92-7.40 (m, 9H, Ar-H)	325.13(M^+)

4f	$C_{17}H_{14}N_2O_3S$	3320, 3050, 3000 cm1, 2520, 1690, 1620, 1600, 1500,1468, 1200, 1180 and 1120	δ 2.1 (s, 1H, -NH-), 3.3 (s,3H, OCH_3), 4.4 (brs 1H, -OH exchangeable with D_2O),4.8 (s,1H,-C=CHAr), 7.1-7.9 (m, 8H, Ar-H)	326.10(M^+)
4g	$C_{17}H_{14}N2$ OS	3320, 3050, 2960, 1690, 1620, 1600, 1500, 1468, 1200 and 1180	^{1}H NMR ($CDCl_3$): δ 1.32 (s, 3H, $-CH_3$), 2.1 (s, 1H, -NH-),4.8 (s 1H, -C=CHAr), 7.2-7.4 (m, 9H, Ar-H)	294.16(M^+)
4h	$C_{17}H_{13}N_2OSCl$	3330,3052, 2960,1695, 1600, 1620, 1500,1460, 1210,1190	δ 1.31 (s, 3H, $-CH_3$) 2.4 (s, 1H, -NH-), 5.2(s, 1H, -C=CH Ar), 7.21-7.51 (m, 8H, Ar-H)	328.10(M^+)
4i	$C_{17}H_{14}N_2$ O_2S	3320,3050, 2950, 2540, 1685, 1618, 1600, 1502, 1468, 1200, 1180 and 1120	δ 1.32 (s, 3H, $-CH_3$),2.2 (s, 1H, -NH-), 4.4(s,1H, -OH exchangeable with D_2O),4.78 (s, 1H,-C=CHAr), 6.9-7.4 (m, 8H, Ar-H)	310.14(M^+)
4j	$C_{18}H_{16}N_2O_2S$	3320, 3050, 3000, 2950, 1690, 1620, 1600, 1500, 1468, 1200, 1180 and 1120	δ 1.31 (s, 3H, $-CH_3$),2.3 (s, 1H, -NH-), 3.3 (s, 3H, $-OCH_3$) , 4.82 (s, 1H, -C=CHAr),7.07-7.76 (m, 8H, Ar-H)	324.18(M^+)
4k	$C_{17}H_{13}N_3O_3S$	1690, 1625, 1600, 1504, 1470, 1210 and 1190	δ 1.33 (s, 3H, $-CH_3$), 2.5(s, 1H, -NH-) ,4.2 (s,1H,-C=CHAr) 6.92-7.40 (m, 8H, Ar-H)	339.16(M^+)
4l	$C_{18}H_{16}N_2O_3S$	3320, 3050, 3000, 2960, 2520, 1690, 1620, 1600, 1500, 1468, 1200, 1180, 1120	δ 1.30(s, 3H, $-CH_3$),2.1(s, 1H, -NH-),3.3 (s, 3H, $-OCH_3$), 4.4 (s,1H, -OH exchangeable with D_2O), 4. 8 (s, 1H,-C=CHAr),7.1-7.9(m, 7H, Ar-H)	340.15 (M^+)

Table 4
Spectral Characterization Data of 1,8-Diaryl-4,8-dihydro-1- Acetyl pyrazolo[3,4-c] imidazol-2- thione (5a-l)

Compd.	Mol. Formula	IR (KBr, υ cm^{-1})	^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)	MS (EI, *m/z* (M^+)
5a	$C_{18}H_{16}N_4OS$	3320,3050,1690, 1640,1600,1500,1468 , 1200, 1180	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H,-$COCH_3$), 3.6 (m, 1H, H-4),5.1 (d, 1H, *J*= 3.2 Hz, H-8),6.46-7.27 (m, 10 H, Ar-H)	336.10(M^+)
5b	$C_{18}H_{15}ClN_4OS$	3330,3050,1690, 1640,1600,1500,1468 , 1200, 1180	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, -$COCH_3$), 3.6 (m, 1H, H-4), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.22 (m, 9 H, Ar-H)	370.5(M^+)
5c	$C_{18}H_{16}N_4O_2S$	3320,3050,2900, 2560,1690,1640,1600 ,1500,1468, 1200, 1180	δ2.0 (d, 1H, J= 2.5 Hz, -NH-),2.02 (s, 3H, -COCH3), 3.6 (m, 1H, H-4), 5.0 (brs, 1H, ArOH exchangeable with D2O), 5.1 (d, 1H, J= 3.2 Hz, H-8),6.46-7.01 (m, 9 H, Ar-H)	352.14(M^+)
5d	$C_{19}H_{18}N_4O_2S$	3320,3050, 2930, 2560,1690,1640,1600 ,1500, 1468, 1200, 1180	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02(s, 3H,-$COCH_3$), 3.6 (m, 1H, H-4), 3.73 (s, 3H, -OCH_3),5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.01 (m, 9 H, Ar-H)	366.16(M^+)
5e	$C_{18}H_{15}N_5O_3S$	3320,3050, 1690, 1640, 1600, 1500, 1468, 1200, 1180	δ 2.0 (d, 1H, *J*= 2.5 Hz,-NH-), 2.02 (s, 3H, -$COCH_3$), 3.6 (m, 1H, H-4),5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-8.14 (m, 9 H, Ar-H)	381(M^+)
5f	$C_{19}H_{18}N_4O_3S$	3320,3050,2930, 2560, 1690, 1640, 1600, 1500, 1468, 1200, 1180, 1120	δ 2.0 (d, 1H, *J*= 2.5 Hz,-NH-), 2.02 (s, 3H, -$COCH_3$), 3.6 (m, 1H, H-4),3.73 (s, 3H, -OCH_3), 5.0 (brs, 1H, ArOH exchangeable with D_2O), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.01 (m, 8H, Ar-H)	381.15(M^+)
5g	$C_{19}H_{18}N_4OS$	3320, 3050, 2930, 1690, 1640, 1600,	δ 2.0 (d, 1H, *J*= 2.5 Hz,-NH-), 2.02 (s, 3H,-$COCH_3$), 2.35 (s, 3H, -CH_3),3.6 (m,	250.10(M^+)

		1500, 1468, 1200, 1180	1H, H-4), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.21 (m, 9H, Ar-H)	
5h	$C_{19}H_{17}ClN_4OS$	3320, 3050, 2940, 1690, 1640, 1600, 1500, 1468, 1200, 1180	δ 2.0 (d, 1H, *J*= 2.5 Hz, - NH-),2.02(s,3H,-$COCH_3$), 2.35 (s, 3H, -CH_3),3.6 (m, 1H, H-4), 5.1(d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.21 (m, 9H, Ar-H)	384.5(M^+)
5i	$C_{19}H_{18}N_2O_2S$	3320, 3050, 2940, 2900, 2560, 1690, 1640, 1600, 1500, 1468, 1200, 1180	δ 2.0 (d, 1H, *J*= 2.5 Hz,-NH-),2.02(s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3),3.6 (m, 1H, H-4), 5.0 (brs, 1H, ArOH exchangeable with D_2O),5.1 (d, 1H, *J*= 3.2 Hz, H-8),6.46-7.01(m, 8H, Ar-H).	366.14(M^+)
5j	$C_{20}H_{20}N_4O_2S$	3320, 3050, 2930, 2900, 1690,1640, 1600,1500, 1468, 1200, 1180, 1120	δ 2.0 (d, 1H, *J*= 2.5 Hz,-NH-), 2.02(s,3H,$COCH_3$), 2.35 (s, 3H, -CH_3),3.6 (m, 1H, H-4), 3.73(s, 3H, -OCH_3), 5.1 (d, 1H,*J*= 3.2 Hz, H-8), 6.46-7.01(m, 8H, Ar-H).	380.16(M^+)
5k	$C_{19}H_{17}N_5O_3S$	3320, 3050, 2930, 1690, 1640, 1500, 1468, 1200, 1180	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, - CH_3),3.6 (m, 1H, H-4), 3.73 (s, 3H,-OCH_3), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-8.14(m, 8H, Ar-H).	395(M^+)
5l	$C_{20}H_{20}N_4O_3S$	3320, 3050, 2930, 2900, 2560, 1690, 1640, 1600, 1500, 1468, 1200, 1180, 1120	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-),2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, - CH_3),3.6 (m, 1H, H-4), 3.73 (s, 3H, -OCH_3), 5.0 (brs, 1H, ArOH exchangeable with D_2O) 5.1 (d, 1H, *J*= 3.2Hz, H-8), 6.46-7.14(m, 7H, Ar-H)	395.15(M^+)

In 1H NMR, there are multiplets at δ 6.46-8.14 due to aromatic protons, singlets at δ 2.02 for -$COCH_3$ protons, doublets at δ 3.60-3.65 with J= 3.2 Hz and at δ 5.1-5.6 with J= 3.2 Hz owing to H-4 and H-8 respectively. The nucleus of pyrazoloimidazol-2-thione was visible in the spectra of 5a–l.

In the IR spectra, there are doublets at δ 2.0 for –NH- with J= 2.5 Hz, singlets at δ 2.00-2.08 for –$COCH_3$, multiplets at δ 3.63 and doublets at δ 4.96 with J= 4.2 Hz due to anomeric proton (C=S). In IR spectra, doublet at δ 2.0 for –NH- with *J*= 2.5 Hz, singlet at δ 2.00-2.08 for –$COCH_3$, multiplet at δ 3.63 for H-4 and doublet at δ 5.1-5.6 with *J*= 3.2 Hz for H-8 and multiplet atδ 6.90-7.80 for aromatic protons supported the formation of 5_{a-l}. Spectra of all the synthesized compounds showed close similaritywith the spectral pattern of fused pyrazolemoiety with 2-thioxoimidazolidine ring.

Singlet at δ 2.02 for -$COCH_3$protons, doublets at δ 3.60-3.65 with *J*= 3.2 Hz and at δ 5.1-5.6 with *J*= 3.2Hz were due to H-4 and H-8 respectively and multiplets at δ 6.46-8.14 were due to aromatic protons in ^{1}H NMR spectra of synthesized compound. ^{13}C NMR spectral analysis in the region δ 108-165 for aromatic carbons and at δ 165-175 for C=S and C=O carbons supported that all synthesized compounds are of pyrazolo-imidazolidin-2-thione skeleton.

Acknowledgement
The authors thank Amity University, Greater Noida, New Delhi for support and CDRI, Lucknow for providing the microanalysis and spectra.

References
1. Abbott A.P., Capper G., Davies D.L., *Chemical Communication*, **1**, 70 **(2003)**

2. Abbott A.P., Davies D.L., Capper G., Rasheed R.K. and Tambyrajah V., Ionic Liquids and their use as solvents, U.S. Patent **(2007)**

3. Abdellatif K.R.A., Fadaly W.A.A., Elshaier Y.A.M.M., Ali W.A.M. and Kamel G.M., *Bioorganic Chemistry*, **77**, 568 **(2018)**

4. Ashok D., Devulapally M.G., Gundu S., Aamate V.K. and Chintalapally S., *Journal of Heterocyclic Chemistry*, **52(8)**, 609 **(2016)**

5. Avalos M., Babiano R., Bravo J.L., Chintas P., Jimenez J.L. and Palacios J.C., *Tetrahedron Letter*, **39(50)**, 9301-9304 **(1998)**

6. Ballini R., Bosica G., Carloni L., Maggi R. and Sartori G., *Tetrahedron Letter*, **39**, 6049–6052 **(1998)**

7. Bandgar B.P., Gawande S.S., Bodade R.G., Gawande N.M. and Khobragade C.N., *Bioorganic Medicinal Chemistry*, **17**, 8168 **(2009)**

8. Bekhit A.A. and Aziem T.A., *Bioorganic Medicinal Chem*istry, **12,** 1935 **(2004)**

9. Ben-Alloum A., Bakkas S. and Soufiaoui M., *Tetrahedron Letter*, **38**, 6395 **(1997)**

10. Bhattacharyya K.G. and Gupta S.S., *Advance in Colloid Interface Science*, **140**, 114-131 **(2008)**

11. Bortolini O., D'Agostino M., De Nino A., Maiuolo L., Nardi M. and Sindona G., *Tetrahedron*, **64**, 8078-8081 **(2008)**

12. Bougrin K., Loupy A., Petit A., Daou B. and Soufiaoui M., *Tetrahedron*, **57**, 163 **(2001)**

13. Brown F.C., Bradsher C.K., Morgan E.C., Tetenbaum M. and Wilder P., *Journal of American Chemical Society,* **78**, 384 **(1956)**

14. Chrysina E.D., Kosmopoulou M.N., Tiraidis C., Kardakaris R., Bischler N., Leonidas D.D., Hadady Z., Somsak L., Docsa T., Gergely P. and Oikonomakos N.G., *Protein Science*, **14(4)**, 873-888 **(2005)**

15. Chunchatprasert L., Rao K.R.N. and Shannon P.V.R., *Journal of Chemical Society, Perkin Transaction,* **1**, 1779-83 **(1992)**

16. Costanzo P., Bonacci S., Cariati L., Nardi M., Oliverio M. and Procopio A., *Food Chemistry,* **245**, 410-414 **(2018)**

17. Costanzo P., Calandruccio C., Di Gioia M.L., Nardi M., Oliverio M. and Procopio A., *Journal of Cleaner Production*, **202**, 504-509 **(2018)**

18. Cravotto G. and Cintas P., *Chemistry: A European Journal*, **13**, 1902-1909 **(2007)**

19. Deng Q. and Wang R., *Catalysis Communication*, **120**, 11-16 **(2019)**

20. Desai K.R., Green Chemistry Microwave Synthesis, 1st ed., Himalaya Publication House, New Delhi, India, 20 **(2005)**

21. DeWitt S.H. and Czarnik A.W., *Accounts of Chemical Research*, **29(3)**, 114-122 **(1996)**

22. Du Mont W.W., Mugesh G., Wismach C. and Jones P.G., *Angewandte Chemie - International Edition*, **40(13)**, 2486-2489 **(2001)**

23. El-Din M.M.G., El-Din M.I., Maksoud M.S.A., Yoo K.H., Baek D., Choi J., Lee H. and Oh C.H., *Journal of Enzyme Inhibition and Medicinal Chemistry*, **31**, 111 **(2016)**

24. Estevão M.S. and Afonso C.A.M., *Tetrahedron Letter,* **58**, 302-304 **(2017)**

25. Fagnoni M., *Heterocycles*, **60**, 1921 **(2003)**

26. Franchetti P., Marchetti S., Capellacci L., Yalowitz J.A., Jayaram H.N., Goldstein B.M. and Grifantini M., *Bioorganic Medicinal Chemistry*, **11**, 67 **(2001)**

27. García J.I., García-Marín H. and Pires E., *Green Chemistry*, **16,** 1007-1033 **(2014)**

28. Goswami M., Dutta M.M. and Phukan P., *Research of Chemical Intermediate,* **44**, 1597-1615 **(2018)**

29. Hechelski M., Ghinet A., Brice Louvel B., Dufrenoy P., Rigo B., Daïch A. and Waterlot C., *ChemSusChem*, **11**, 1249-1277 **(2018)**

30. Horikoshi S. and Serpone N., *Catalysis Science and Technology*, **4**, 1197-1210 **(2014)**

31. Huang Q., Tran G., Pardo D.G., Tsuchiya T., Hillebrand S., Vors J.P. and Cossy J., *Tetrahedron*, **71**, 7250 **(2015)**

32. Hughes A., Hendrikson R.G., Chen B.C. and Valento M., *American Journal of Emergence Medicine*, **36**, 1527 **(2018)**

33. Jaselnik M., Varma R.S., Polanca S. and Kocevar M., *Chemical Communication*, **18**, 1716-1717 **(2001)**

34. Kappe O., *Angewandte Chemie International Edition*, **43**, 6250-6284 **(2004)**

35. Kaur N. and Kishore D., *Journal of Chemical and Pharmaceutical Research,* **4**, 991-1015 **(2012)**

36. Kumar B.S., Dhakshinamoorthy A. and Pitchumani K., *Catalysis Science and Technology*, **4**, 2378-2396 **(2014)**

37. Lapkin A., Plucinski P.K. and Cutler M., *Journal of Natural Product*, **69**, 1653-1664 **(2006)**

38. Li J.T., Xing C.Y. and Li T.S., *Journal of Chemical Technology and Biotechnology*, **79**, 1275-1278 **(2004)**

39. Maiuolo L., De Nino A., Algieri V. and Nardi M., *Mini-Review Organic Chemistry*, **14**, 136-142 **(2017)**

40. Majumdar K.C., Basu P.K. and Mukhopadhyay P.P., *Tetrahedron* ,**60**, 6239 **(2004)**

41. Mason T.J., *Philosophical Transaction of the Royal Society London, A*, **357**, 355-369 **(1999)**

42. Mc Gee D.P.C., Martin J.C., Smee D.F and Verheyden J.P.H., *Nucleosides and Nucleotides*, **9**, 815 **(1990)**

43. Nardi M., Di Gioia M.L., Costanzo P., De Nino A., *Catalysts*, **7**, 269 **(2017)**

44. Nardi M., Herrera Cano N., Costanzo P., Oliverio M., Sindona G. and Procopio A., *RSC Advance*, **5,** 18751-18760 **(2015)**

45. Nardi M., Herrera Cano N., De Nino A., Di Gioia M.L., Maiuolo L., Oliverio M., Santiago A., Sorrentino D. and Procopio A., *Tetrahedron Letter,* **58**, 1721-1726 (**2017)**

46. Oliverio M., Costanzo P., Macario A., De Luca G., Nardi M. and Procopio A.A., *Molecules*, **19,** 10218-10229 **(2014)**

47. Oliverio M., Costanzo P., Nardi M., Calandruccio C., Salerno R. and Procopio A., *Beilstein Journal of Organic Chemistry*, **12**, 2222-2233 **(2016)**

48. Oliverio M., Costanzo P., Paonessa R., Nardi M. and Procopio A., *RSC Advance*, **3**, 2548-2552 **(2013)**

49. Oliverio M., Nardi M., Cariati L., Vitale E., Bonacci S. and Procopio A., *ACS Sustainable Chemical Energy*, **4**, 661-665 **(2016)**

50. Onoa G.B. and Moreno V., *Internation Journal of Pharmaceutics, 2***45**, 55 **(2002)**

51. Osman A.I., Abu-Dahrieh J.K., McLaren M., Laffir F. and Rooney D.W., *Chemistry Select*, **3**, 1545-1550 **(2018)**

52. Paiva A., Craveiro R., Aroso I., Martins M., Reis R.L. and Duarte A.R.C., *ACS Sustainable Chemical Engineering*, **2**, 1063-

1071 **(2014)**

53. Pal D., Saha S. and Singh S., *Internation Journal of Pharmacy and Pharmaceutical Science,* **4**, 98 **(2012)**

54. Porcu A., Melis M., Turecek R., Ullrich C., Mocci I., Bettler B., Gessa G.L. and Castelli M.P., *Neuropharmacology*, **133**, 107 **(2018)**

55. Poupaert J.H., Bukuri J. and Gozzo A., *Monatshefte fur Chemie*, **130**, 929 **(1999)**

56. Procopio A., De Luca G., Nardi M., Oliverio M. and Paonessa R., *Green Chemistry*, **11**, 770-773 **(2009)**
57. Procopio A., Gaspari M., Nardi M., Oliverio M. and Rosati O., *Tetrahedron Letter*, **49**, 2289-2293 **(2008)**

58. Rajanarendar E., Afzal M. and Karunakar D., *Indian Journal of Chemistry,* **42B**, 353 **(2003)**

59. Rosario A., Andres J.I., Lopez M.T., Heras F.G., Herranz R., Alarcon B. and Carrasco L., *Journal of Medicinal Chemistry*, **28**, 834 (**1985)**

60. Rostamizadeh S., Amani A.M., Aryan R., Ghaieni H.R. and Norouzi L., *Monatshefte für Chemie*, **140,** 547-552 **(2009)**

61. Roudier J.F. and Foucaud A., *Tetrahedron Letter*, **25**, 4375 **(1984)**

62. Salimi M., Ghahremani M.H., Naderi N., Amini M., Salimi E., Amanlou M., Abdi K., Salehi R. and Shafiee A., *Acta Pharmacological Sinica*, **28(8)**, 1254-1260 **(2007)**

63. Senthilkumar S., Maru M.S., Somani R.S., Bajaj H.C. and Neogi S., *Dalton Transaction,* **47**, 418-428 **(2018)**

64. Shaikh N.S., Gajare A.S., Deshpande V.H. and Bedekar A.V., *Tetrahedron Letter*, **41**, 385 **(2000)**

65. Shi C., Ma C., Ma H., Zhou X., Cao J. and Fan Y., *Tetrahedron*, **72**, 4055-4058 **(2016)**

66. Sieskind O., Albrecht P., *Tetrahedron Letter*, **34**, 1197 **(1993)**

67. Siu Y. A., Hao M. H., Dixit V. and Lai W.G., *Drug Metabolism and Pharmacokinetics*, **33(5)**, 219–227 **(2018)**

68. Thomas J.M., Raja R. and Lewis D.W., *Angewandte Chemie International Edition*, **44**, 6456 **(2005)**.

(Received 21st May 2024, accepted 25th July 2025)