SYNTHESIS AND CHARACTERIZATION OF SOME BIOLOGICALLY IMPORTANT 1-ISOPROPYL INDAZOLYL THIADIAZOLE, TRIAZOLE AND OXADIAZOLE BY COVENTIONAL AND NONCONVENTIONAL METHODS

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Abstract: Compound **1** on treatment with $SOCl_2$ followed by hydrazine hydrate gave acid hydrazide **2.** Variously substituted phenyl isothicyanates with acid hydrazide **2** gave thiosemicarbazides **3**. These thiosemicarbazides **3** on treatment with Conc. H_2SO_4 and dil. NaOH gave thiadiazoles **4** and triazoles **5** respectively. Compound **3** on treatment with I_2 in KI, in presence of NaOH gives oxadiazole **6**.

Introduction

According to the literature survey, indazole compounds are associated with various physiological and biological properties and thus find important use in medicine. Indazole compounds are capable of mediating tyrosine kinase signal transduction and their by inhibit unwanted cell proliferation[1, 2]. Indazole derivatives are examined for analgesic-anti-inflammatory activity[3]. A ruthenium co-ordination complex (Rulnd) is one the most effective anticancer[4] ruthenium compound; poisoning[5] of Topoisomerase II by indazole complex is analysed. Indazole ring was used as the initial template to test the hypothesis in order to increase potency as Leukotriene receptor antagonists[6, 7, 8].Indazole containing inhibitor series for SAH/MTA nucleosidase are inhibitors with broad spectrum antimicrobial activity[9]. Indazole derivatives are used as anti-inflammatory agents[10], anticancer[10, 11] agents and also used as sunscreens[12].

Thiosemicarbazide are found to be associated with antibacterial[13], antifungal[14] herbicidal[15], antiacetyl cholinesterase[16] and antituburcular[17] activities.

Compounds containing 1,3,4-thiadiazole nucleus have been reported to a variety of biological activities like fungitoxic[18], CNS stimulant[19],anticholinergic[20], hypoglycemia[21], and anticonvulsant[22,23]. Some of the thiadiazole derivatives are found to be associated with spasmolytic activites[24] and anti-inflammatory activities[24].

Triazoles are known for their fungicidal[25], pesticidal[26], tranquiliser and sedative[27] properties. Triazoles are an important class of heterocyclic compounds.They express antifungal[28], bactericidal[28,29] , anxiolytic[30,31], anticonvulsant[32] or herbicidal[33] activities or can act as intidepressants[34].

Several oxadiazoles and thiadizoles also exhibit antitubercular[35], antifungal[36] and herbicidal[36] properties.

The advantageous use of ultra sound irradiation technique for activating various reactions is well documented in the literature such as synthesis of azoles and diazenes[37], reformatsky reaction[38], oxidation of substrates like hydroquinones[39], conversion of nitro compounds to carbamates[40], pinacol coupling[41], Ullmann condensation[42], Suzuki cross coupling[43] etc.

Over past few decades, the many significant advances in the practical aspects of organic chemistry have included novel strategies and methods as well as the advent of a vast array of analytical techniques[44]. It was first reported that organic reactions could be accelerated in domestic microwave ovens[45, 46].

The use of unaltered domestic microwave oven as a convenient source of energy in organic synthesis is now well establishised procedure[47, 48]. Using microwaves rapid heating of the reactants can be achieved, owing to substantial reduction in the reaction period. Many of the reactions have been carried out in open vessels using polar solvents such as alcohol, water, DMF etc. as the energy transfer media, which absorbs microwave energy through dipole rotation. But reactors would be required for the reaction and they needed to be capable of reliable and safe operation with volatile organic solvents, at elevated temperatures and pressures.

Biological activities associated with indazole, thiosemicarbazide, thiadizole, triazole and oxadiazole moieties and advantages of sonochemical and microwave synthesis prompted us to synthesize some oxadiazole, thadiazole and triazole with indazole nucleus by sonochemical and microwave methods.

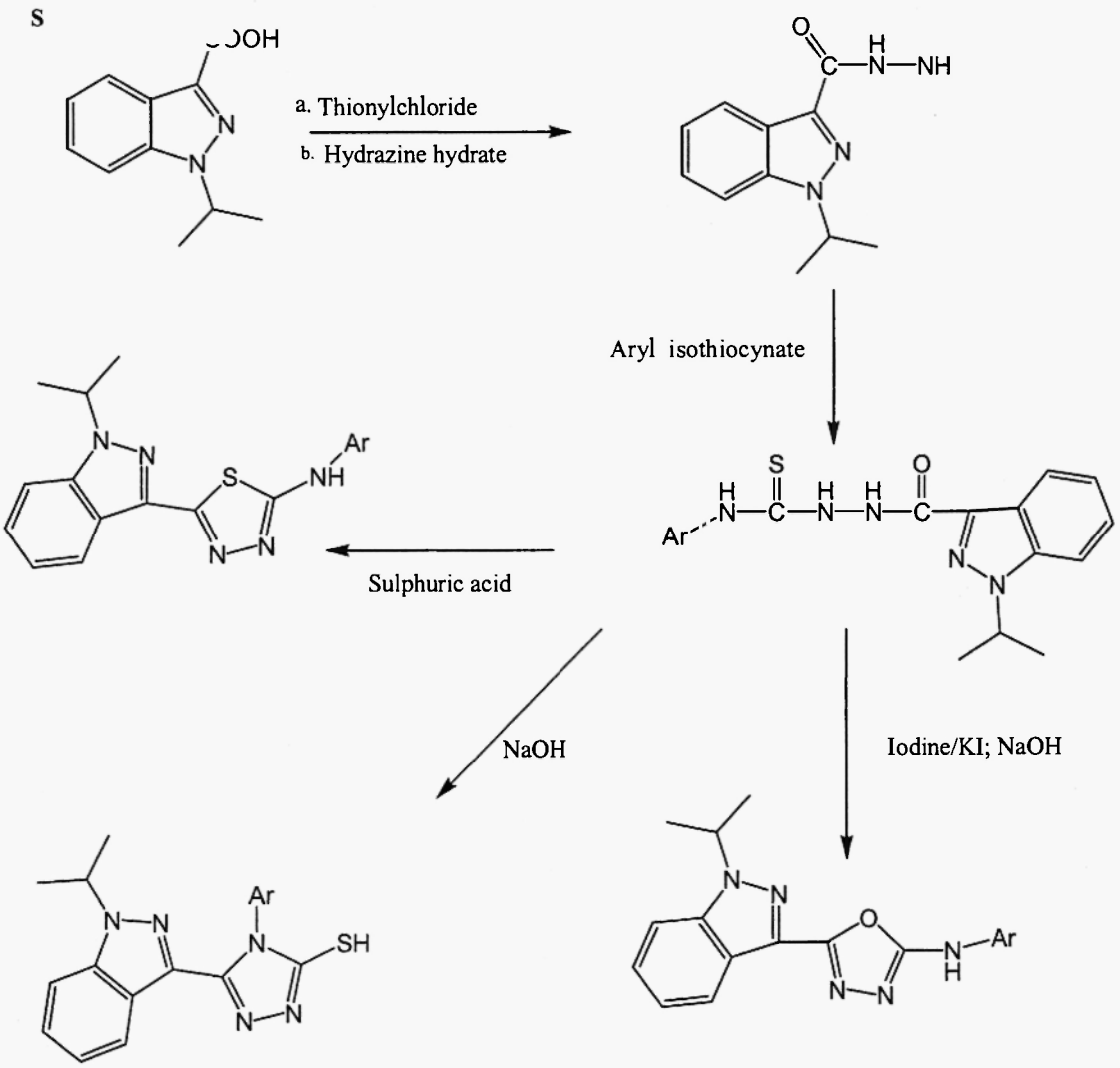
Results and Discussions

In present work acid **1** was treated with thionyl chloride followed by treatment with methanol and then hydrazine hydrate to get the acid hydrazide **2**. Acid hydrazide **2** when treated with aryl isothiocyanates under ultra sound and microwave irradiation gave the compounds **3**, these compounds **3** in acidic medium under ultra sound and microwave irradiation gave compounds **4** i.e. thiadiazoles and in basic medium under ultra sound and microwave irradiation gave compounds **5** i.e. triazoles. Compounds **3** on treatment with I_2 in KI gives Amino-oxadiazole **6** (Scheme-1)

Compound **3** shows the characterstic absorption peaks at 3257 cm^{-1}, 1673 cm^{-1}, 1192 cm^{-1} due to N-H, -C=O and -C=S functionality respectively. ^1H NMR shows characterstic peaks due to –N-H protons at 9.5δ, s, 9.6δ, s, and 10.35δ, s. The structures of these compounds are also confirmed by their mass spectra. For compound **4** IR absorption peak at 3250cm^{-1} due to –N-H functionality, ^1H NMR shows signal at 10.4δ due to –N-H proton. The structures of these compounds are also confirmed by mass spectra. For compound **5** IR absorption peak at 1600 cm^{-1}due to –C=N functionality. Compound **5** ^1H NMR shows signal at 14.2δ due to –S-H proton. The structures of these compounds are also confirmed by mass spectra. For compound **6** IR absorption peak at 3253 cm^{-1} and 1582 cm^{-1} due to –N-H and –C=N functionality. The structures of these compounds are also confirmed by mass spectra.

Experimental

All the recorded melting points were determined in open capillary tubes and are uncorrected. I.R. spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc. ^1H NMR spectra were recorded on Varian 300 MHz spectrophotometer in DMSO as a solvent and TMS as an internal standard. Peak values are shown in δ ppm. Mass spectra were obtained by Finnigan mass spectrometer. Experiment under ultrasound irradiation was carried out in ultrasonic cleaner model EN-20U-S manufactured by ENERTECH ELECTRONICS PVT.LTD, Mumbai, India having maximum power output of 100W and 33 KHz operating frequency and under microwave irradiation using commercial microwave oven (BPL, 800T, 2450 MHz).



Scheme-1

1[(1-Isopropyl-1H-indazole-3-yl)carbonyl]-4-phenyl thiosemicarbazide(3a-i):

Method (A) By conventional method: Equimolar amount (0.01 mole) of acid hydrazide (**2**) and aryl isothiocyanates (0.01 mole) was taken in 100 ml RBF with 15 ml ethanol. Reaction mixture was heated under reflux for 45 minutes. Progress of reaction was monitored with the help of TLC. After completion of reaction product obtained was separated by filtration. The product was crystallized from ethanol. This typical experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by above procedures are listed in **Table 1** with their characterization data. Their structures have been confirmed by IR, NMR and mass spectra.

Method (B) By ultra sound method: Equimolar amount (0.01 mole) of acid hydrazide (**2**) and aryl isothiocyanates (0.01 mole) was taken in 100 ml RBF with 15 ml ethanol. Reaction mixture was subjected for ultra sound irradiation for 20 minutes. Progress of reaction was monitored with the help of TLC. After completion of reaction product obtained was separated by filtration. The product was crystallized from ethanol. This typical experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by above procedures are listed in **Table-1** with their characterization data.

Method (C) By microwave method: A mixture of acid hydrazide (**2**) (0.01 mole) , (0.01mole) of aryl isothiocynate and ethanol (25ml) was irradiated in a borosilicate glass beaker (50 ml) inside a microwave oven for 90-120 Sec at an output of 300 watts power, with short interruption of 15 Sec to avoid excessive evaporation of solvent. Progress of reaction was monitored by TLC. The reaction mixture was cooled and poured in to ice water. Product was separated by filtration and crystallized with alcohol to afford the titled compounds. Their characterization and spectral data is given in the **Table-1** and **2.**

5-(1-Isopropyl-1H-indazol-3-yl)-N-phenyl-1,3,4-thiadiazol-2-amine(4a-i):
Method (A) By conventional method: Thiosemicarbazide (**3**) (0.01 mole) was taken in 100 ml RBF with 15 ml conc. H_2SO_4. The Reaction mixture was well stirred at RT for 2 hours and then poured into crushed ice. The solid thus obtained was separated by filtration and crystallized from water /DMF afforded title compounds. The compounds synthesized by above procedures are listed in **Table-1** with their characterization data. Their structures have been confirmed by IR, NMR and mass spectra as listed in **Table-2**.

Method (B) By ultra sound method: Thiosemicarbazide (**3**) (0.01 mole) was taken in 100 ml RBF with 15 ml conc. H_2SO_4. Reaction mixture was subjected for ultra sound irradiation for 20 minutes. Progress of reaction was monitored with the help of TLC. After completion of reaction contents were poured into crushed ice. Product obtained was separated by filtration. The product was crystallized from DMF/water. This typical experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by above procedures are listed in **Table 1** with their characterization data.

Method (C) By microwave method: Thiosemicarbazide (**3**) (0.01 mole) was taken in 50 ml borosilicate glass beaker with 15 ml conc. H_2SO_4. Reaction mixture was irradiated inside a microwave oven for 2 min to 2.5 min at an output of 300 watts power, with short interruption of 15 second. Progress of reaction was monitored by TLC. The reaction mixture was cooled and poured into crushed ice. Product was separated by filtration and crystallized with DMF / water to afford the titled compounds. Their characterization and spectral data is given in **Table 1** and **2** with their characterization and spectra data respectively.

5-(1-Isopropyl-H-indazol-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol(5a-f):
Method (A) By conventional method: Thiosemicarbazide (**2**) 0.005 mole and 10 ml of 2N sodium hydroxide solution was heated under mild reflux for 1.5 hours. Progress of reaction was monitored by TLC. The reaction mixture was cooled and poured into crushed ice and acidified with dilute acetic acid. Product was separated by filtration and crystallized with DMF/water to afford the titled compounds. This typical experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by above procedures are listed in **Table 1** with their physical constants, percentage yields. Their structures have been confirmed by IR, NMR and mass spectra as listed in **Table 2.**

Method (B) By ultra sound method: Thiosemicarbazide (**3**) (0.01 mole) was taken in 100 ml RBF with 10 ml 2N sodium hydroxide solution. Reaction mixture was subjected for ultra sound irradiation for 30 minutes. Progress of reaction was monitored with the help of TLC. After completion of reaction contents were poured into crushed ice. Product obtained was separated by filtration. The product was crystallized from DMF/water. This typical experimental procedure was followed to prepare other analogs of this series. The compounds synthesized by above procedures are listed in **Table 1** with their characterization data.

Method (C) By microwave method: Thiosemicarbazide (**3**) (0.01 mole) was taken in 50 ml borosilicate glass beaker with 10ml 2N sodium hydroxide solution. Reaction mixture was irradiated inside a microwave oven for 2 min to 2.5 min at an output of 300 watts power, with short interruption of 15 second. Progress of reaction was monitored by TLC. The reaction mixture was cooled and poured into crushed ice. Product was separated by filtration and crystallized with DMF / water to afford the titled compounds. Their characterization and spectral data is given in the listed in **Table 1** and **2** with their characterization and spectral data.

5-(1-Isopropyl-1H-indazol-3-yl)-N-phenyl-1,3,4-oxadiazol-2-amine(6a-h):
By conventional method: Thiosemicarbazide (**3**) (0.01 mole) and 4N NaOH 2ml was refluxed for 4 hrs in ethanol 200 ml and (2.5g) iodine in 10 ml of KI (3.2gm) solution added to it , till the colur of iodine persisted. The reaction mixture was concentrated, cooled and the solid is filtered and crystallized from ethanol. Their characterization and spectral data is given in the table listed **Table-1** and **Table-2.**

Table-1: Characterization data of the synthesized compounds.

Compd No.	Ar group	m.p.	(Yield time) for US			(time Yield) for µW		(time-Yield) traditional	
		°C	(%)	(min)		(min)	(%)	(min)	(%)
3a	Phenyl	177	85	20		1.5	87	40	85
3b	2-Methoxyphenyl	184	94	20		1.5	89	35	72
3c	3-Methoxyphenyl	157	82	20		2.0	80	45	70
3d	4-Methoxypheny l	195	85	20		2.0	85	40	87
3e	2-Methylphenyl	176	89	20		2.0	80	45	78
3f	3-Methylphenyl	175	84	20		1.5	85	40	86
3g	4-Methylphenyl	178	85	20		1.5	79	45	73
3h	3-Chlorophenyl	162	86	30		2.0	78	40	74
3i	4-Chlorophenyl	148	80	20		2.0	75	40	72
4a	Phenyl	219	86	20		2.5	81	120	70
4b	2-Methoxyphenyl	300	81	20		2.5	74	120	73
4c	3-Methoxyphenyl	240	78	20		2.5	78	120	72
4d	4-Methoxyphenyl	200	84	20		2.0	70	120	69
4e	2-Methylphenyl	270	81	20		2.5	74	120	60
4f	3-Methylphenyl	249	82	20		2.0	73	120	69
4g	4-Methylphenyl	290	80	20		2.0	83	120	72
4h	3-Chlorophenyl	315	75	20		2.0	68	120	71
4i	4-Chlorophenyl	265	80	20		2.5	73	120	70
5a	Phenyl	291	75	30		2.5	70	90	63
5b	3-Methoxyphenyl	185	73	35		2.5	70	90	68
5c	4-Methoxyphenyl	246	75	30		2.5	71	90	70
5d	2-Methylphenyl	216	68	30		2.0	65	90	72
5e	3-Methylphenyl	246	75	30		2.0	64	90	60
5f	4-Methylphenyl	271	72	35		2.5	68	90	69
6a	Phenyl	165	--	--		--	--	240	65
6b	2-Methoxyphenyl	140	--	--		--	--	240	60
6c	3-Methoxyphenyl	132	--	--		--	--	240	70
6d	4-Methoxyphenyl	185	--	--		--	--	240	67
6e	2-Methylphenyl	186	--	--		--	--	240	72
6f	3-Methylphenyl	151	--	--		--	--	240	66
6g	4-Methylphenyl	156	--	--		--	--	240	60
6h	3-Chlorophenyl	136	--	--		--	--	240	66

All compounds showed satisfactory elemental analysis.

Table-2: Spectral data of the synthesized compounds.

Compd	Ar-group	Spectral data (NMR in δ ppm, IR values in cm^{-1} &mass given as M^+.
3a	Phenyl	IR: 3259, 1678, 1528, 1485, 1200, 755. NMR: 1.35δ, d, 6H, 5.0δ, m, 1H, 6.8 to 8.1δ,m, 9H, 9.2δ, s, 1H, 9.4δ, s, 1H & 9.8δ, s, 1H, Mass M^+=354.
3b	2-Methoxyphenyl	IR: 3245, 1672, 1520, 1477, 1185, 745. NMR:1.6δ, d, 6H, 4.35δ, s, 3H, 5.6δ, m, 1H, 7.3δ, to 8.4δ, m, 8H, 9.71δ, s, 1H, 9.9δ, s, 1H & 10.45δ,s, 1H, Mass M^+=384.
3c	3-Methoxyphenyl	IR: 3245, 1672, 1521, 1478, 1184, 748, NMR: 1.58δ,d, 6H, 4.4δ,s,3H, 5.5 δ, m,1H, 7.3 to 8.4 δ, m, 8H, 9.68δ, s, 1H, 9.8δ, s, 1H & 10.4δ, s, 1H, Mass M^+=384.
3d	4-Methoxyphenyl	IR: 3240, 1668, 1520, 1477, 1180, 745, NMR: 1.62δ,d, 6H, 4.45 δ,s,3H, 5.8 δ, m,1H, 7.35 to 8.4δ, m, 8H, 9.75δ, 1H, 9.9δ, s, 1H & 10.45 δ, s, 1H, Mass M^+ = 384.
3e	2-Methylphenyl	IR: 3257, 1674, 1524, 1481, 1192, 750, NMR: 1.5δ,d, 6H, 2.25 δ,s,3H, 5.2 δ, m,1H, 7.2 to 8.2 δ, m, 8H, 9.5δ, s, 1H, 9.6δ, 1H & 10.35 δ, s, 1H, Mass M^+=368.
3f	3-Methylphenyl	IR: 3256, 1673, 1524, 1480, 1190, 749, NMR: 1.45δ,d, 6H, 2.20 δ,s,3H, 5.1 δ, m,1H, 7.2δ to 8.1δ, m, 8H,9.4δ, s,1H, 9.5δ, s, 1H & 10.3 δ, s, 1H, Mass M^+=368.
3g	4-Methylphenyl	IR: 3259, 1674, 1525, 1480, 1190, 750, NMR: 1.5δ, d, 6H, 2.3δ, s, 3H, 5.3δ, m,1H, 7.3 to 8.4 δ, m, 8H, 9.5δ,s,1H,9.6δ, s, 1H & 10.4δ, s, 1H, Mass M^+=368.
3h	3-Chlorophenyl	IR: 3260, 1680, 1530, 1484, 1196, 755, NMR: 1.7δ,d, 6H, 5.5 δ, m,1H, 7.4 to 8.5 δ, m, 8H, 9.5δ, s, 1H,9.7δ, s, 1H & 10.45δ, s, 1H, Mass M^+=388.
3i	4-Chlorophenyl	IR: 3262, 1682, 1530, 1484, 1196, 754, NMR: 1.6δ,d, 6H, 5.6 δ, m,1H, 7.4 to 8.5 δ, m, 8H, 9.6δ, s, 1H,9.72 δ,s, 1H & 10.5 δ, s, 1H, Mass M^+=388.
4a	Phenyl	IR: 3250, 1573, 1503, 1454, 741. NMR: 1.5δ, d, 6H, 5.15δ, m, 1H, 7.0 to 8.3 δ, 9H & 10.6δ, s, 1H, Mass M^+=336.
4b	2-Methoxyphenyl	IR: 3240, 1570, 1498 1448, 740. NMR: 1.61δ, d, 6H, 3.8δ, s, 3H, 5.4δ, m, 1H, 7.5 to 8.5δ, 8H &10.7δ, s, 1H, Mass M^+=366.
4c	3-Methoxyphenyl	IR: 3242, 1571, 1495, 1450, 738. NMR: 1.6δ, d, 6H, 4.0δ, s, 3H, 5.35δ, m, 1H, 7.5 to 8.4 δ, 8H & 10.65δ, s, 1H, Mass M^+=366.
4d	4-Methoxyphenyl	IR: 3235, 1569, 1498, 1450, 735. NMR: 1.6δ, d, 6H,4.2δ, s, 3H, 5.40δ, m, 1H, 7.6 to 8.5 δ, 8H & 10.7δ, s, 1H, Mass M^+=366.
4e	2-Methylphenyl	IR: 3240, 1571, 1500, 1452, 740. NMR: 1.55δ, d, 6H,2.7δ,s ,3H, 5.25δ, m, 1H, 7.2 to 8.2 δ, 8H & 10.65δ, s, 1H, Mass M^+=350.
4f	3-Methylphenyl	IR: 3242, 1571, 1499, 1450, 736. NMR: 1.58δ, d, 6H, 2.6δ, s, 3H, 5.3δ, m, 1H, 7.1 to 8.25 δ, 8H & 10.64δ, s, 1H, Mass M^+=350.
4g	4-Methylphenyl	IR: 3238, 1570, 11498, 1450, 740. NMR: 1.55δ, d, 6H, 2.8δ, s, 3H, 5.3δ, m, 1H, 7.2 to 8.4 δ, 8H & 10.68δ, s, 1H, Mass M^+=350.

Table-2 (Cont'd): Spectral data of the synthesized compounds.

4h	3-Chlorophenyl	IR: 3255, 1578, 1510, 1474, 765. NMR: 1.55δ, d, 6H, 5.3δ, m, 1H, 7.3 to 8.3 δ, 8H & 10.68δ, s, 1H, Mass M^+=370.
4i	4-Chlorophenyl	IR: 3259, 1580, 1516, 1460, 768. NMR: 1.58δ, d, 6H, 5.35δ, m, 1H, 7.3 to 8.4 δ, 8H & 10.7δ, s, 1H, Mass M^+=370.
5a	Phenyl	IR: 3089, 1510, 1458, 1299, 745. NMR: 1.2δ, d, 6H, 4.9δ, m, 1H, 7.2 to 8.2δ, m, 9H & 14.2δ, s, 1H, Mass M^+=336.
5b	3-Methoxyphenyl	IR: 3078, 1500, 1451, 1289, 735. NMR: 1.4δ, d, 6H, 4.2δ, s, 3H, 5.35δ, m, 1H, 7.35 to 8.45δ, m, 8H & 14.4δ, s, 1H, Mass M^+=366.
5c	4-Methoxyphenyl	IR: 3073, 1495, 1445, 1284, 730. NMR: 1.52δ, d, 6H, 4.4δ, s, 3H, 5.5δ, m, 1H, 7.4 to 8.5δ, m, 8H & 14.6δ, s, 1H, Mass M^+=366.
5d	2-Methylphenyl	IR: 3080, 1500, 1453, 1291, 739. NMR: 1.35δ, d, 6H, 2.6δ, s, 3H, 5.2δ, m, 1H, 7.3 to 8.4δ, m, 8H & 14.35δ, s, 1H, Mass M^+=350.
5e	3-Methylphenyl	IR: 3083, 1506, 1455, 1295, 743. NMR: 1.3δ, d, 6H, 2.4δ, s, 3H, 5.0δ, m, 1H, 7.3 to 8.3δ, m, 8H & 14.25δ, s, 1H, Mass M^+=350.
5f	4-Methylphenyl	IR: 3078, 1498, 1450, 1290, 742. NMR: 1.4δ, d, 6H, 2.8δ, s, 3H, 5.3δ, m, 1H, 7.35 to 8.4δ, m, 8H & 14.35δ, s, 1H, Mass M^+=350.
6a	Phenyl	IR: 3253, 1637, 1604, 1582, 749. NMR: 1.6δ, d, 6H, 5.2δ, m, 1H, 7.0 to 8.25δ, m, 10H, Mass M^+=319.
6b	2-Methoxyphenyl	IR: 3244, 1630, 1595, 1575, 740. NMR: 1.95δ, d, 6H, 3.9δ, s, 3H, 5.85δ, m, 1H, 7.3 to 8.4δ, m, 9H, Mass M^+= 350.
6c	3-Methoxyphenyl	IR: 3248, 1630, 1600, 1577, 745. NMR: 1.90δ, d, 6H, 4.1δ, s, 3H, 5.72δ, m, 1H, 7.25 to 8.45δ, m, 9H, Mass M^+=350.
6d	4-Methoxyphenyl	IR: 3242, 1628, 1592, 1571, 735. NMR: 1.9δ, d, 6H,4.35δ, s, 3H, 5.9δ, m, 1H, 7.4 to 8.6δ, m, 9H, Mass M^+=350.
6e	2-Methylphenyl	IR: 3246, 1632, 1600, 1576, 742. NMR: 1.8δ, d, 6H, 2.7δ, s, 3H, 5.5δ, m, 1H, 7.2 to 8.45δ, m, 9H, Mass M^+=334.
6f	3-Methylphenyl	IR: 3248, 1634, 1601, 1579, 744. NMR: 1.75δ, d, 6H, 2.5δ, s, 3H, 5.4δ, m, 1H, 7.2 to 8.4δ, m, 9H, Mass M^+=334.
6g	4-Methylphenyl	IR: 3245, 1630, 1598, 1575, 740. NMR: 1.75δ, d, 6H, 2.65δ, s, 3H, 5.55δ, m, 1H, 7.3 to 8.5δ, m, 9H, Mass M^+=334.
6h	3-Chlorophenyl	IR: 3258, 1643, 1610, 1592, 758. NMR: 1.8δ, d, 6H, 5.7δ, m, 1H, 7.5 to 8.5δ, m, 9H, Mass M^+=354.

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